Coordination Chemistry Reviews 255 (2011) 1623–1641

Contents lists available at ScienceDirect

Coordination Chemistry Reviews

journal homepage: www.elsevier.com/locate/ccr

Reviews

Recent advances of discrete coordination complexes and coordination polymers in drug delivery

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Contents

ARTICLE INFO

Article history:
Received 21 October 2010
Accepted 12 January 2011
Available online 25 January 2011

ABSTRACT

Coordination complexes (including discrete coordination complexes and coordination polymers) have demonstrated excellent performance in drug delivery. This review outlines recent advances of discrete coordination complexes, bulk coordination polymers, and nanoscale/microscale coordination polymers in drug delivery. Specifically, rationale and mechanism of coordination complexes in drug delivery are

Abbreviations: ADMET, absorption, distribution, metabolism, excretion, and toxicity; AL, ancillary ligand; API, active pharmaceutical ingredient; ASP, aspirin and copper(II)–aspirinate complexes; BBB, blood–brain barrier; BCS, Biopharmaceutics Classification System; BDC, terephthalic acid; bix, 1,4-Bis(imidazol-1-ylmethyl)benzene; CNS, central nervous system; CPs, coordination polymers; CPT, camptothecin; CUS, coordinatively unsaturated metal sites; DAU, daunomycin; DDSs, drug delivery systems; DFT, density functional theory; DLS, dynamic light scattering; DOSY, diffusion ordered NMR spectroscopy; DOX, Doxorubicin; DSCP, disuccinatocisplatin; ESCP, *c,c,t*-[$PtCl_2(NH_3)_2(OEt)(O_2CCH_2CH_2CO_2H)$]; ESI-MS, electrospray ionization mass spectrometry; FDA, Food and Drug Administration; GRAS, generally recognized as safe; IBU, Ibuprofen; IIG, Inactive Ingredient Guide; LDH, layered double hydroxide; MCPs, microscale coordination polymers; MIL, Materials of Institut Lavoisier; MOFs, metal-organic frameworks; MOPs, metal-organic polyhedra; NCPs, nanoscale coordination polymers; NMEs, new molecular entities; NO, nitric oxide; NSAIDs, nonsteroidal anti-inflammatory drugs; PBS, phosphate-buffered saline; PEG, Polyethylene glycol; PIB, powder in bottle; PVP, Polyvinyl pyrrolidone; SAS, salsalate and copper(II)–salsalate complexes; SBF, simulated body fluid; SBU, secondary building units; SEDDS, self-emulsifying drug delivery system; SEM, scanning electron microscope; SR, solubility ratio; XRPD, X-ray powder diffractions.

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0010-8545/$ – see front matter
doi:10.1016/j.ccr.2011.01.031

Keywords:
Drug delivery
Coordination
Supramolecular
Metal-organic frameworks
Nanoscale
Pharmaceutical

summarized in this contribution. In this review, we discuss applications of these coordination species in drug delivery from perspectives in chemistry and pharmaceutical sciences, and an outlook of these coordination species of interest in drug delivery will also be proposed.

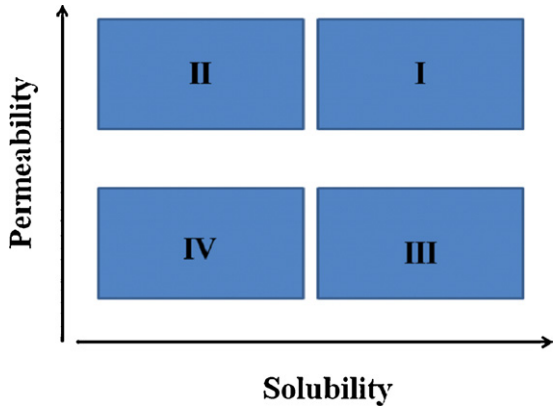


Fig. 1. Biopharmaceutical Classification System (BCS) of drugs based on solubility and permeability.

1. Introduction

For decades, tremendous effort has been devoted to the study of coordination complexes, including discrete coordination complexes and coordination polymers (CPs), for their utilitarian properties and interesting structures [1–6]. The rapid development of materials science and crystal engineering has considerably promoted the uses of coordination complexes as functional materials such as catalysts, magnetic materials, non-linear optical materials and porous materials [7–11]. It is not surprising that pharmaceutical scientists, biologists, medicinal and inorganic chemists have also been engaged in the research of coordination complexes for biomedical applications, for instance, metal-based drugs and imaging agents [12–14]. Particularly, applications of discrete and polymeric coordination complexes in drug delivery have received great attention from a variety of researchers, and a large number of accomplishments have been achieved in recent years. This review covers recent advances of coordination complexes in drug delivery within the past 10 years, specifically highlighting rationale, mechanism and outlook for coordination complexes in drug delivery. This review is intended to provide an overview for researchers interested in this area.

Drug delivery is an extremely broad area of research, embracing a variety of activities such as fine-tuning physical–chemical properties of active pharmaceutical ingredients (APIs), targeted drug delivery to the proper site of action, control of drug release kinetics, and design of drug formulations. In this review, we will focus on applications of coordination complexes in drug delivery. For other coordination systems, e.g., transition metal-based drugs and transition metal-based diagnostic agents, readers are referred to corresponding literature [15–20]. To obtain a full appreciation of how discrete coordination complexes and coordination polymers can be applied as drug delivery systems (DDSs), we must turn first to some recent challenges in developing novel drug delivery systems.

In 1995, Amidon and co-workers proposed the Biopharmaceutics Classification System (BCS) [21], which categorizes orally administered drugs into four classes according to their solubility and permeability (Fig. 1). The permeability of a drug can be measured by the Caco-2 permeability assay [22,23] and, often enough, can be estimated from its lipophilicity value – the partition coefficient (log *P*) [24,25]. It is fairly clear that BCS class I drugs can provide good *in vivo* bioavailability and may bring ease to early stage clinical trials at lower cost simply in the form of powder in a bottle (PIB) or powder in capsules. BCS class II drugs have low aqueous solubility; however, the problem of the low solubility is often manageable by judicious formulation designs such as spray drying [26], micronization [27], self-emulsifying drug delivery system (SEDDS) [28] and forming inclusion compounds with β-cyclodextrin [29]. For BCS class III and class IV drugs, there are very few formulation strategies to improve the lipophilicity/permeability. A more realistic approach is to go back to the lead optimization stage which can be very time-consuming and costly. In fact, there is a tendency that more and more clinical drug candidates fall into the categories of BCS class III and class IV these days. Therefore, there is a great necessity to develop new approaches to rationally modify the lipophilicities of drugs, the final purpose of which is to control the drug delivery pattern accordingly. In such a context, our group has recently reported the novel approach of mixed-ligand coordination species dealing with the rational modification of lipophilicities [30–32].

Another challenge present in the pharmaceutical industry is to control the drug release in order to acquire the optimum therapeutic efficacy. Indeed, not all drugs are suitable for administration as immediate-release dosage forms. The controlled release of drugs is often needed for two major reasons: (1) the drug molecule has a short half life *in vivo*, which results in having to dose multiple times daily to maintain the therapeutical levels; and (2) the drug molecule may have a narrow therapeutic index with negative side effects associated with its peak plasma concentrations. In the pharmaceutical industry, controlled drug release is often realized by means of either polymer matrices or multiparticulate systems for oral dosage forms [33–35]. Both approaches are widely used nowadays in the pharmaceutical industry. The release kinetics of a drug depends on many factors: grade of polymers, drug loading levels, in-process parameters, and formulation techniques. One drawback of these two industrial approaches is that the as-developed drug delivery systems often require multi-step formulation procedures (milling, granulation, coating, tabletting, etc.) such that the final product could have a relatively high risk to fail after exposure to the high temperature and humidity in process. Moreover, it is often difficult in practice to strictly control the drug release kinetics, for example, zero order, "Higuchi", first order and so on [36].

With these limitations of current industry-applied controlled drug delivery systems, and with the recent emergence of advanced materials engineering and nanotechnology, many materials have been proposed and studied as drug delivery carriers in the past decade. Traditional DDS materials can be classified into organic DDSs and inorganic DDSs. Organic DDSs such as polymeric systems and liposome-based systems normally have good biocompatibility but often boast no controlled release in the absence of a well-defined porosity [37–42]. While inorganic DDS materials such as microporous zeolites, mesoporous silicon and layered double hydroxide (LDH) are able to release drug molecules in a controlled manner, their applications in drug delivery are often restricted by their limited loading capacity [43–48]. Férey and co-workers first introduced the third route – using "hybrid" inorganic–organic

coordination polymers as DDSs [49]. Coordination polymers, also known as metal-organic frameworks (MOFs), are a new class of materials composed of transition metals and organic ligand linkers. Motivated by Férey and co-workers' pioneering work, a number of research groups have also investigated applications of coordination polymers in drug delivery. A great many achievements have been made in this field to date, which are summarized in this review.

2. Discrete coordination complexes in drug delivery

In the pharmaceutical industry, the discovery of new molecular entities (NMEs) involves the derivatization of lead compounds or drug candidates via covalent organic transformations. With the rapid evolution of supramolecular synthesis [50–52], using supramolecular chemistry approaches to modify APIs has become a topical area in supramolecular chemistry and crystal engineering. In the context of supramolecular synthesis, there exist two primary design elements: hydrogen bonds and coordination bonds. Pharmaceutical co-crystals utilizing the hydrogen bond approach managed to gain industrial recognition during formulation studies [53–56]. Our (Moulton) group has developed a novel approach to modify the lipophilicity and solubility of transition metal-containing drugs by forming mixed-ligand coordination species [30–32], in which the ancillary ligand is introduced by coordination bonds. There are also other types of weaker supramolecular interactions such as π–π interactions and van der Waals force. The combination of weaker supramolecular interactions may be used as a supramolecular chemistry approach for drug delivery in some specific cases as well [57].

2.1. Mixed-ligand Cu^{II} complexes

Compounds containing nonsteroidal anti-inflammatory drugs (NSAIDs) as ligands in Cu^{II} complexes are known [58–60]. Moreover, they have exhibited both enhanced efficacy and reduced side effects. Moulton and Ma first developed an approach to rationally modify the lipophilicity and solubility of Cu-NSAIDs species by forming mixed-ligand coordination complexes [30]. By tuning the lipophilicity and solubility of a drug complex, its drug delivery pattern should be modified accordingly.

2.1.1. Can "additive–constitutive properties" be extended to coordination complexes?

The lipophilicity and solubility of a drug are not only key parameters that influence its absorption, distribution, metabolism, excretion, and toxicity (ADMET) properties but also essential factors to be considered at the formulation development stage [61,62]. 1-Octanol/water partition coefficient P is commonly used as the suitable estimate of lipophilicity [63–65]. A range of log *P* generally exists for a certain class of drugs to obtain the optimal medicinal efficacy; for example, the optimal log *P* value is about 2 for a central nervous system (CNS) drug's passive penetration through the blood–brain barrier (BBB) [66].

It is well-established that partition coefficients (log *P*) have an additive–constitutive character within a congeneric series of compounds prepared from a parent organic drug [67]. In the contribution by Moulton and co-workers, a systematic effort toward understanding *in vitro* structure-activity relationships for drug-metal complexes was carried out. Several homologous series of mixed-ligand Cu^{II} coordination complexes were synthesized by the introduction of ancillary ligands (ALs). As can be seen in Table 1, the order of log *P* values for the Cu^{II}–ASP–AL complexes with the same type of coordination chromophore reflects the order of log *P* values calculated for the ancillary ligands, which is qualitatively consistent with the additive–constitutive character observed for organic congeners. Table 1 only demonstrated the results when AL is neutral. A similar trend was also reported in this study when AL is anionic.

2.1.2. Other factors affecting lipophilicities and solubilities of coordination complexes

A coordination complex is a more complicated system than a pure organic molecule because of the existence of transition metals. Transition metals may accommodate different coordination chromophore in the solid state, and the coordination complexes may also experience transformations of molecular configurations when dissolved in water. Therefore, there are a lot of other factors affecting lipophilicities of coordination complexes. In the study by Moulton and co-workers, (1) coordination chromophore, (2) hydrogen bond, and (3) size effect were also determined as key factors which could produce significant effects on lipophilicities of mixed-ligand coordination complexes.

In Tables 1 and 2, APIs present in these complexes are in their anionic forms. As can be seen in Table 1, the complexes that possess the dicopper chromophore are more lipophilic than the monocopper complexes. ESI-MS of complexes ASP-5, 6 and 8 suggest that the monocopper complex exists as a hydrated species, $Cu(ASP)_2(AL)_2(H_2O)$, in the aqueous phase. This presumably increases the aqueous solubility and thus decreases its relative lipophilicity. The effect of hydrogen bonds can be examined by comparing complexes ASP-(6-8) with ASP-5, the log *P* order of which does not follow the log *P* order of ancillary ligands. In complexes ASP-(6-8), amide is a very good hydrogen bond donor and acceptor [68]. It has been suggested that hydrogen bonding reduces the relative affinity for the aqueous phase over the octanol phase, and thus increases the relative lipophilicity [69]. Therefore, hydrogen bonding explains the discrepancy. Size effect can be illuminated clearly by looking into the lipophilicity data of a series of Cu–SAS–AL compounds, Table 2. Although the log *P* values calculated for the ancillary ligands vary in a wide range (from −0.282 to 2.715), only SAS-4 and SAS-5 showed significantly increased log *P* values via the introduction of aromatic ancillary ligands. This is attributed to the size effect of ancillary ligands. As exemplified in Fig. 2, the ancillary ligands were sterically shielded by salsalate phenol rings, and notably SAS-2 and SAS-5 showed interesting "molecular sandwich" structures. Even though 4-benzylpyridine and 4-phenylpyridine are also sterically shielded by salsalate phenol rings in some fashion, the lipophilicities of corresponding complexes SAS-4 and SAS-5 were still considerably enhanced for the exceptionally large molecular size of ancillary ligands.

Based on the reported solubility values, there is also some degree of predictability in observed aqueous solubility based on the log *P* of the ancillary ligand. In general, the lower the log *P* value of the ancillary ligand is, the higher aqueous solubility of corresponding mixed-ligand coordination species would be.

2.2. Mixed-ligand Zn^{II} complexes

Most recently, Moulton and co-workers demonstrated that the approach of forming mixed-ligand coordination complexes could also be applied to Zn^{II} coordination systems [32]. In this work, a Zn^{II} compound with insulin-mimetic effects – $Zn(PNO)_2$ was chosen as the starting material [70], where HPNO stands for 2-hydroxypyridine N-oxide. A homologous series of mixed-ligand Zn^{II} coordination complexes were synthesized by the introduction of ancillary ligands. Coordination mode of the ancillary ligand was determined to be another key factor for the modification of coordination complexes. Unlike Cu^{II} complexes, monodentate ancillary ligand is not suitable to modify the lipophilicity of a Zn^{II} coordination species due to its poor stability in water. Therefore, bidentate ancillary ligands were used in this work and showed reasonable

Table 1
Formula, coordination chromophore of aspirin and complexes ASP-(1-9), and their solubilities and partition coefficients at 25 °C, Ref. [30].

	Complex formula	Coordination chromophore	log *P* of AL[a]	S_w (mg/ml)	log *P* of complex
Aspirin (**ASP**)	/	/	/	4.600	1.321(25)
ASP-1	$Cu_2(ASP)_4$	4 coordinate *paddle-wheel*	/	3.414(25)	−0.2371(267)
ASP-2	$Cu_2(ASP)_4(DMF)_2$	5 coordinate *paddle-wheel*	−1.010(277)	3.092(33)	−0.3484(166)
ASP-3	$Cu_2(ASP)_4(3\text{-Br-Py})_2$	5 coordinate *paddle-wheel*	1.751(286)	1.564(3)	0.1066(58)
ASP-4	$Cu_2(ASP)_4(Quinoline)_2$	5 coordinate *paddle-wheel*	2.084(195)	2.729(1)	0.4772(140)
ASP-5	$Cu(ASP)_2(Pyridine)_2$	4 coordinate *square planar*	0.726(178)	3.425(21)	−0.7001(111)
ASP-6	$Cu(ASP)_2(Isonicotinamide)_2(AcCN)_2$	4 coordinate *square planar*	−0.282(289)	9.315(10)	−0.4647(274)
ASP-7	$Cu(ASP)_2(Isonicotinamide)_2$	4 coordinate *square planar*	−0.282(289)	9.259(5)	−0.4723(272)
ASP-8	$Cu(ASP)_2(Nicotinamide)_2$	4 coordinate *square planar*	−0.110(237)	4.417(50)	−0.5257(136)
ASP-9	$Cu(ASP)_2(3\text{-Phenyl-Pyridine})_2$	4 coordinate *square planar*	2.600(244)	0.5415(7)	0.9106(312)

[a] log *P* of ancillary ligands were calculated using Advanced Chemistry Development (ACD/Labs) Software V8.14 for Solaris.

Table 2
Formula, coordination chromophore of salsalate and complexes SAS-(1-9), and their solubilities, and partition coefficients at 25 °C, Ref. [31].

	Complex formula	Coordination chromophore	log *P* of AL[a]	S_w (mg/ml)	log *P* of complex
Salsalate (**SAS**)	/	/	/	0.59[a]	3.045(353)[a]
SAS-1	$Cu_2(SAS)_4(H_2O)_2$	5 coordinate *paddle-wheel*	/	0.2791(6)	0.06927(1394)
SAS-2	$Cu_2(SAS)_4(caffeine)_2$	5 coordinate *paddle-wheel*	−0.131(371)	0.3405(20)	0.05420(695)
SAS-3	$Cu_2(SAS)_4(3\text{-Cl-Pyridine})_2$	5 coordinate *paddle-wheel*	1.569(214)	0.1239(1)	0.06467(1468)
SAS-4	$Cu_2(SAS)_4(4\text{-Benzyl-Pyridine})_2$	5 coordinate *paddle-wheel*	2.715(199)	0.0134(3)	0.7481(870)
SAS-5	$Cu_2(SAS)_4(4\text{-Phenyl-Pyridine})_2(THF)_2$	5 coordinate *paddle-wheel*	2.590(242)	0.0303(3)	1.231(53)
SAS-6	$Cu(SAS)_2(Pyridine)_3$	5 coordinate *square pyramidal*	0.726(178)	0.4065(8)	0.03218(199)
SAS-7	$Cu(SAS)_2(Isonicotinamide)_2(AcCN)_{2/3}$	4 coordinate *square planar*	−0.282(289)	0.3143(9)	0.03802(967)
SAS-8	$Cu(SAS)_2(4\text{-Me-Pyridine})_2$	4 coordinate *square planar*	1.186(185)	0.2301(18)	0.01407(1658)
SAS-9	$Cu(SAS)_2(4\text{-Et-Pyridine})_2$	4 coordinate *square planar*	1.718(185)	0.1143(2)	0.02089(576)

[a] log *P* of ancillary ligands were calculated using Advanced Chemistry Development (ACD/Labs) Software V8.14 for Solaris.

stabilities in the aqueous phase, as confirmed by diffusion ordered NMR spectroscopy (DOSY) [71–74] results. In this contribution, it was also demonstrated that there is some degree of predictability in the observed lipophilicities and solubilities of mixed-ligand Zn^{II} coordination complexes on the basis of log *P* of the ancillary ligand. More importantly, given the previously reported data in Cu^{II} coordination systems, the results in this work suggested the approach of forming mixed-ligand species to modify lipophilicities and solubilities of coordination complexes with medicinal properties can be applied to a wide range of transition metal coordination systems.

2.3. Supramolecular assembly of discrete coordination complexes

Instead of forming mixed-ligand coordination species through coordination bonds, multiple discrete coordination complexes could also form supramolecular assembly through even weaker intermolecular forces such as hydrophobic forces, van der Waals forces, π–π interactions and electrostatic effects. Liu and coworkers recently demonstrated a triad supramolecular array with useful applications in drug delivery [57]. The triad supramolecular array is composed of two discrete coordination complexes: Zn[4-amino-N-(2-methylquinolin-8-yl)benzenesulfonamide-modified permethyl-β-cyclodextrin (MQAS-PMCD)]$_2$ (denoted as Zn**1**$_2$) and Zn[meso-tetrakis-(4-sulfonatophenyl)-porphyrin (TSPP)] (denoted as ZnTSPP). In the aqueous phase, a linear triad Zn**1**$_2$–ZnTSPP supramolecular array was formed through strong association between the β-cyclodextrin cavity and the anionic porphyrin (Scheme 1). The supramolecular interactions between the β-cyclodextrin cavity and the anionic porphyrin not only prevent the unfavorable porphyrin-porphyrin aggregation but also ensure the high stability of such supramolecular systems in biological environments. When the triad supramolecular assembly was inter-

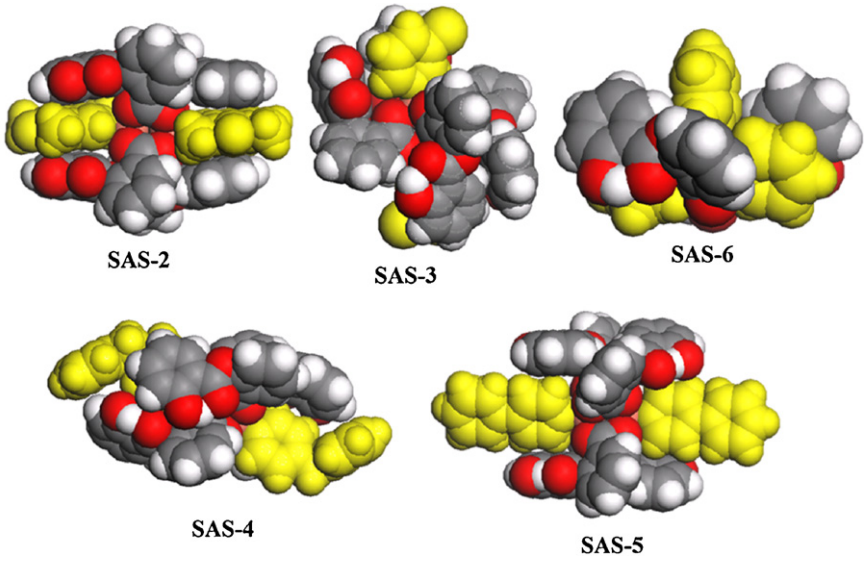
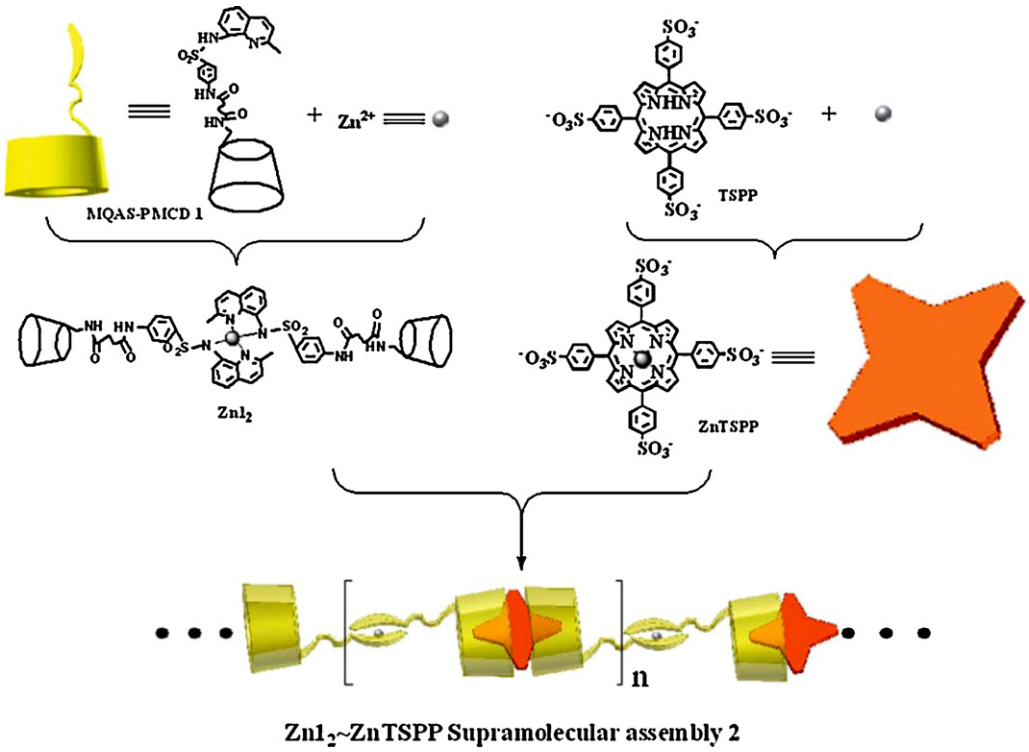


Fig. 2. Single-crystal structure units of complexes SAS-(2-6) in CPK mode; ancillary ligands were labeled with yellow for clarity.



Scheme 1. Schematic illustration of the linear triad Zn**1**$_2$–ZnTSPP supramolecular array. Reprinted from Ref. [57]. Copyright 2010, with permission from the Royal Society of Chemistry.

acting with the cells, the array was disrupted due to the change in the environment (from the aqueous phase to the hydrophobic environment of cell lipid layers). Subsequently, Zn**1**$_2$ remained in the cell membrane, while the porphyrin component-ZnTSPP entered the cells. It is noteworthy that the efficiency of delivering ZnTSSP into the cells by the triad supramolecular assembly was significantly higher than that of the free ZnTSSP. Liu also proposed such supramolecular systems may be used to deliver drug molecules with anionic porphyrin skeletons such as β-octaphenyl-*meso*-tetra(4-carboxyl)-phenylporphyrin and its derivatives. The drug delivery mechanism of such triad supramolecular arrays is still not quite clear based on the preliminary data and therefore deserves further investigations.

2.4. Summary and outlook

The strategy of forming mixed-ligand coordination complexes has provided a general and rational approach to modify the lipophilicity and solubility of transition metal-based drugs or organic drugs which could act as ligands in a coordination species. The latter requires the incorporation of non-toxic transition metals. There are some other advantages of the approach of introducing ancillary ligand through coordination bonds over altering the parent drug compound via organic transformations: easy preparation, integrity of the API, concomitant purification and lower cost. It is also worth noting that a coordination complex Cu_2(ibuprofen)$_4$(caffeine)$_2$ containing two active ingredients (Ibuprofen and Caffeine) was synthesized by Mouton and co-workers [31]. Therefore the "mixed-ligand coordination complexes" approach might be considered as a potential route to prepare "Two-in-One" or "Three-in-One" drug products. These *proof-of-principle* mixed-ligand coordination complexes showed reasonable stabilities in deionized water. Future research of mixed-ligand coordination complexes should be dedicated to their stabilities and bioavailabilities in biological fluids. Liu's work demonstrated a combination of weaker intermolecular forces could be used to form supramolecular assemblies to improve the drug delivery efficiency [57].

One of the anticipated concerns regarding the use of metal-based coordination species may be the toxicity of transition metals and ancillary ligands. With regards to the toxicity of transition metals, it should not be an issue if the parent drug is transition metal-based, e.g., Cisplatin [75], because the toxicity of transition metal should have already been addressed; low-toxic or non-toxic metals such as Fe, Zn, Ca [76,77], and Ti [78] should be used if the approach is used to modify physical–chemical properties of the organic drug ligand only [79]. It is suggested that the daily intake of certain transition metals under the Tolerable Upper Intake level is supposed to pose no risk of adverse health effects for almost all individuals in the general population [79]. With regards to the toxicity of ancillary ligands, we suggest that "generally recognized as safe" (GRAS) substances and ingredients listed by E Number Index (A list of additives currently permitted in food within the European Union) such as acetic acid, citric acid and nicotinamide should be considered as the first choice. Use of some non-GRAS substances (e.g., caffeine) as ancillary ligands may follow the Food and Drug Administration (FDA) Inactive Ingredient Guide (IIG).

Besides the above, there is a special type of discrete coordination complexes – metal-organic polyhedra (MOPs) or nanoballs [80–82] that have great potentials to be used as drug delivery carriers. MOPs generally have nanometer scale dimensions and possess high symmetry. One obvious advantage of MOPs over regular nano-materials is that the dimension of the MOP supermolecule is strictly uniform. MOPs have attracted much interest over the past 10 years. Most published MOPs reports are concentrated on their structures and gas storage properties [83]. However, to the best of our knowledge, examples of MOPs as drug delivery systems have not been reported to date. There are 2 reasons that make it feasible for MOPs to be applied in drug delivery. First, MOPs can form large inner cavities. For

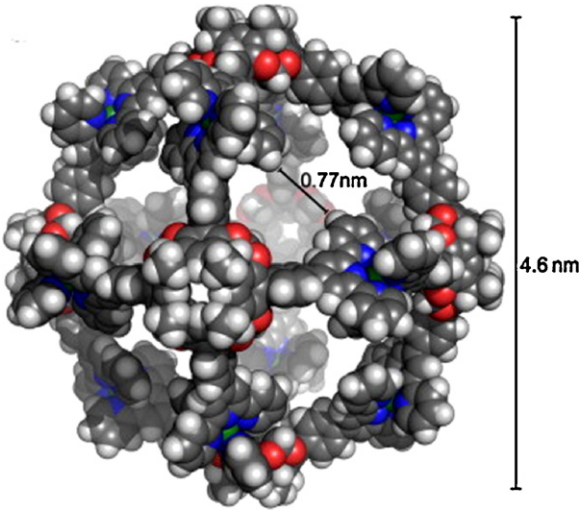


Fig. 3. Space-filling representation of the O-symmetric MOP. Reprinted from Ref. [84]. Copyright 2008, with permission from Elsevier.

example, Mattay and co-workers demonstrated a cuboctahedron MOP in which 6 cavitands are bridged by Zn-terpyridine linkages (Fig. 3) [84]. This MOP exhibits an outer diameter of *ca.* 4.6 nm with large aperture of *ca.* 7.7 Å which correspond to a volume of about 13.7 nm^3. Mattay also estimated that anions may fit into the inner cavity. Therefore, the large cavity volume and aperture window size might make this material suitable for adsorption of some small molecule drugs by ion exchange. The second reason is more interesting. Organic molecules can be mounted on MOPs by postsynthesis. Volkmer and co-workers reported a postsynthetic reaction on nanoballs [85]. This study highlights the feasibility of introducing organic species onto MOPs by postsynthesis. In addition, Volkmer reported that nanoballs were very kinetically stable in solution. Han and Moulton have also demonstrated the postsynthesis of discrete Cu–Carboxylate coordination complexes by click reactions [86]. Functionalities such as $–NH_2$, –OH, and –OR on the shell of nanoballs provide chemists a lot of opportunities to decorate MOPs. Meanwhile organic molecules, including some small molecule drugs, can be possibly connected to MOPs by postsynthetic modifications. Based on the promising preliminary results, we envisage that MOPs would be applied as a new type of drug delivery carrier in the future.

3. Bulk coordination polymers in drug delivery

Coordination polymers are often referred as hybrid inorganic–organic materials. Coordination polymers consist of transition metal ions/clusters and multidentate organic ligands. In addition to their basically simple chemical compositions, they have acquired properties from both inorganic materials and organic materials. For coordination polymers, many typical properties of inorganic materials such as magnetic, electronic and thermal properties are generally derived from transition metals [87–89]; and organic ligands often contribute to these characteristic properties that usually organic materials have, such as the biocompatibility and polymer properties [90,91]. This explains why coordination polymers often have more superior and unique functional properties compared to pure inorganic materials or organic materials. With this in mind, researchers have explored the application of coordination polymers in drug delivery in recent years. The great potential of using coordination polymers as DDSs largely relies on a number of factors: (1) high surface area and porosity [92]; (2) low toxicities of certain transition metals, i.e. Fe, Zn; (3) good physical and chemical stabilities [93,94]; and (4) well-defined chemical compositions.

3.1. Delivery of drug molecules

3.1.1. Adsorption/desorption-type coordination polymers as drug delivery systems

In 2006, Férey and co-workers reported the first *proof of principle* example of utilizing coordination polymers in drug delivery [49]. Two mesoporous coordination polymers, Chromium-based MIL-100 and MIL-101 (MIL, Materials of Institut Lavoisier) [95,96] were selected as drug carriers for Ibuprofen (IBU). They were dehydrated prior to Ibuprofen adsorption. X-ray powder diffractions (XRPD) of both materials confirmed that their framework structures are retained. N_2 adsorption after the drug adsorption experiments indicated almost no residual porosity. Both materials showed remarkable drug loadings: MIL-100 with 35% (w/w) of Ibuprofen/carrier and MIL-101 with 140% (w/w) of Ibuprofen/carrier. The high drug loading, particularly in the case of MIL-101, facilitates reducing the final dosage weight at constant active pharmaceutical ingredient (API) strength. The discrepancy of drug adsorption performance between MIL-100 and MIL-101 is attributed to differences of their crystal structures (Fig. 4). Two types of spherical cages exist in MIL-100 and MIL-101. The first type of cage consists of pentagonal windows, while the second type consists of both pentagonal and hexagonal ones. Dimensions of the free window apertures explain the considerably different drug adsorptions in MIL-100 and MIL-101 [in MIL-100, 4.8 × 5.8 Å (pentagonal), 8.6 Å (hexagonal); in MIL-101, 12 Å (pentagonal), 14.7 × 16 Å (hexagonal)]. Considering that the size of Ibuprofen is around 6 × 10.3 Å, apparently the smaller cages in MIL-100 are not accessible for Ibuprofen. In contrast, the large pore size of both types of cages in MIL-101 facilitates easy introduction and high uptake of Ibuprofen. The adsorbed Ibuprofen was in the anionic form. The drug release experiments were performed in simulated body fluid (SBF) at 37 °C. Both materials showed "two-stage" release profiles. For MIL-100, the initial zero order release of weakly bound drug molecules within the first 2 h was observed, followed by a sustained drug release within 3 days. For MIL-101, the "Higuchi" type release governed by drug diffusions occurred within the first 8 h, followed by the sustained drug release within 6 days.

These two drug release stages are directly related to host–guest interactions. Jiang and co-workers reported a computation study of the energetics and dynamics of Ibuprofen in MIL-101 [97]. Jiang's work suggested a coordination bond is formed between Ibuprofen and Cr (in MIL-101), consistent with the broadening of NMR signals of Ibuprofen as reported in Férey's work. The binding energy between Ibuprofen and MIL-101 matrix was reported by Jiang to be 73.17 kJ/mol. Jiang also suggested that when the surrounding regions of Cr centers were saturated by drug molecules as the drug loading increased, then the subsequently adsorbed Ibuprofen would experience weaker interactions (π–π interactions, van der Waals force, etc.). This explains the first stage of fast drug release and the following stage of sustained drug release in both cases.

In a more recent study by Férey and co-workers, flexible coordination polymers as DDSs were reported [98]. The work concerned two porous coordination polymers – MIL-53(Cr) and MIL-53(Fe) [99], which exhibited drug loading capacity and which were flexible upon the adsorption of guest molecules. The MIL-53 solids were dehydrated prior to Ibuprofen adsorption. Because of the breathing effect, the symmetry of crystalline solids changed from monoclinic to orthorhombic with the expansion of the cell volume after the adsorption of drug molecules. In addition, the structures of filled MIL-53(Cr) and MIL-53(Fe) are identical according to their XRPD patterns. Both MIL-53 materials could adsorb up to 20% (w/w) of Ibuprofen/carrier. The drug release experiments were performed

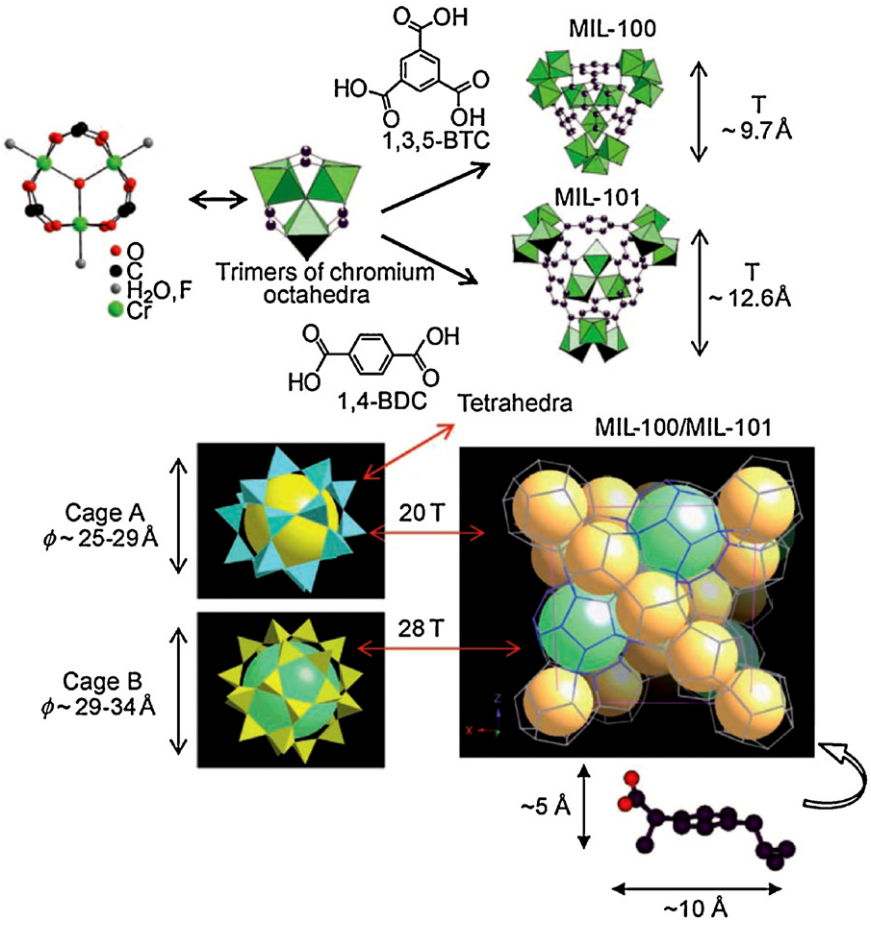


Fig. 4. (Top) Schematic 3D representation of the tetrahedra (T) built up from trimers of chromium octahedra and 1,4-benzenedicarboxylate moieties or 1,3,5-benzenetricarboxylate groups in MIL-101 and MIL-100, respectively. (Bottom) Schematic 3D representation of the mobil-39 (MTN)zeotype architecture of MIL-100 and MIL-101; left: the smaller A cages(yellow spheres with 20 T) and larger B cages (green spheres with 28 T); right: a unit cell (lines connect the T centers). Reprinted from Ref. [49]. Copyright 2006, with permission from Wiley-VCH Verlag GmbH & Co. KGaA.

in SBF at 37 °C. A zero order drug release kinetics was observed for MIL-53(Cr) and MIL(Fe) within 3 weeks. Their drug release profiles were similar except there was a short period of fast release followed by a pseudo plateau in the case of MIL-53(Fe). The implication of this discrepancy was that the nature of the metal center could produce some influence on the first step of the delivery. XRPD patterns of MIL-53 solids before and after the drug release remained the same. Férey suggested that the invariance of cell parameters could be attributed to the exchange between the drug molecules and some species from the SBF medium. The adsorbed Ibuprofen was in the neutral form. The DFT calculations indicated strong hydrogen bonding between the oxygen of the carboxylic group of Ibuprofen and hydroxyl group of the host matrix. The optimized drug-MIL-53(Fe) matrix interaction was calculated to be 57 kJ/mol.

Rosi and co-workers reported experiments dealing with cation-triggered drug release from a Zinc–Adeninate coordination polymer [100]. In this contribution, the containing coordination polymer $[Zn_8(ad)_4(BPDC)_6O{\cdot}2Me_2NH_2, 8DMF, 11H_2O]_n$ (ad, adeninate; BPDC, biphenyldicarboxylate), referred to as bio-MOF-1, was synthesized as the drug carrier. The ligand adenine was chosen as a ligand partly for its well-developed coordination capacity and partly for its biocompatibility. The host matrix of bio-MOF-1 has the **pcu** topology (Fig. 5). The host matrix network is anionic with dimethylamine cations and solvent molecules in the open channel. Rosi and co-workers chose procainamide·HCl as the model drug. Drug loading of procainamide·HCl into bio-MOF-1 was performed by multi-steps of cation exchange experiments. Similar to the MIL class materials, XRPD indicated that the drug loading process did not affect the crystalline integrity of bio-MOF-1. Bio-MOF-1 could achieve 22% (w/w) of drug loading (procainamide·HCl/carrier), comparable to MIL-53. The drug release experiments were performed in 0.1 M phosphate-buffered saline (PBS) (pH = 7.4) at room temperature. More than 70% of drug was released within 20 h, and complete release was realized in 3 days (Fig. 6). However, only 20% of procainamide was released in a comparative experiment of bio-MOF-1 in deionized water (Fig. 6). The parallel control experiments verified that procainamide release was mediated by the buffer cations.

3.1.2. Biodegradable coordination polymers as drug delivery systems

Recently another drug delivery approach was developed by Serre and co-workers by forming biodegradable therapeutic coordination polymers, in which the bioactive molecule – vitamin B3 was the ligand coordinated to non-toxic Fe [101]. It is a positive advantage that the API itself acts as the ligand because no additional drug loading steps are needed. The content of vitamin B3 is 71.5% w/w in the Fe-vitamin B3 coordination polymer (BIOMIL-1) by its formula. The drug release experiments were performed in PBS (pH = 7.4) at 37 °C. Fast release of vitamin B3 was realized by the degradation of the coordination polymer. Complete drug release was achieved in 1 h.

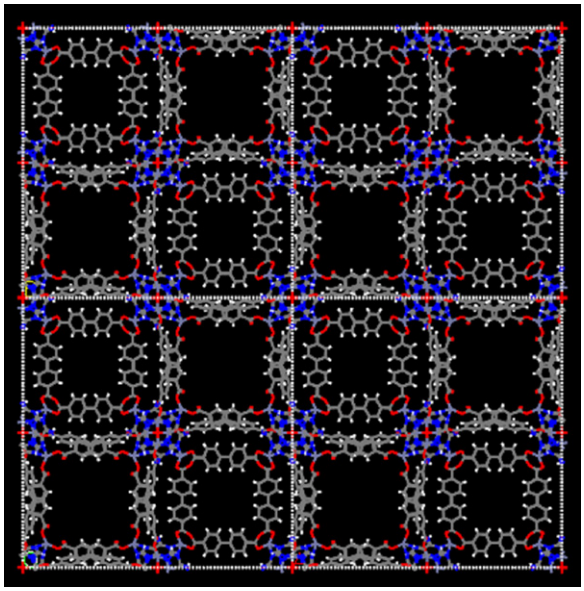


Fig. 5. The single crystal structure of bio-MOF-1 viewed along the crystallographic *c* axis.

3.2. Delivery of nitric oxide (NO) molecules

Nitric oxide (NO) plays an essential role in the cardiovascular, nervous and immune systems [102]. Solid NO carriers have potential biomedical applications for their anti-bacterial, anti-thrombic and wound healing properties [103–106]. Herein we review the delivery of NO using coordination polymers in a separate section, reasons being that unlike regular drug molecules in either solid or liquid state, NO is a gas at normal temperature and pressure. Due to the obvious differences in molecular weight and dimensions of NO and small molecule drug, the delivery mechanism and release kinetics of these species of interest in coordination polymers could vary considerably. A variety of organic or inorganic materials such as polymers, nanoparticles and zeolites have been explored as NO delivery platforms [104,107–112]. Liaw and co-workers reported a discrete dinitrosyl Fe coordination compound, which may serve as NO-donor species [113]. Therefore, coordination polymers were also brought to the notice of researchers as NO delivery carriers for their high surface areas and porosity and well-defined chemical compositions. Fortunately, gas storage and release utilizing coordination polymers as carriers have been extensively studied in recent years and have gradually become technologically mature [11,114], which can provide scientists a good starting point to carry out similar research (in this case, using coordination polymers to deliver a specific bioactive molecule – NO).

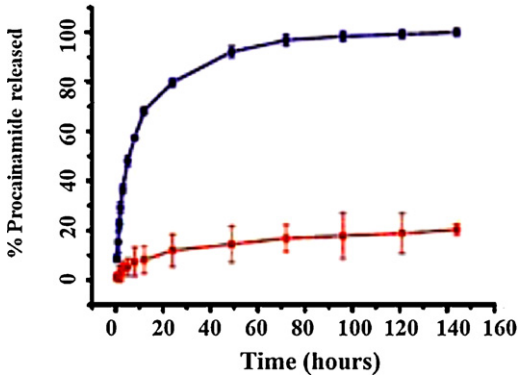


Fig. 6. Procainamide release profiles from bio-MOF-1 (blue, PBS buffer; red, deionized nanopure water). Reprinted from Ref. [100]. Copyright 2009, with permission from American Chemical Society.

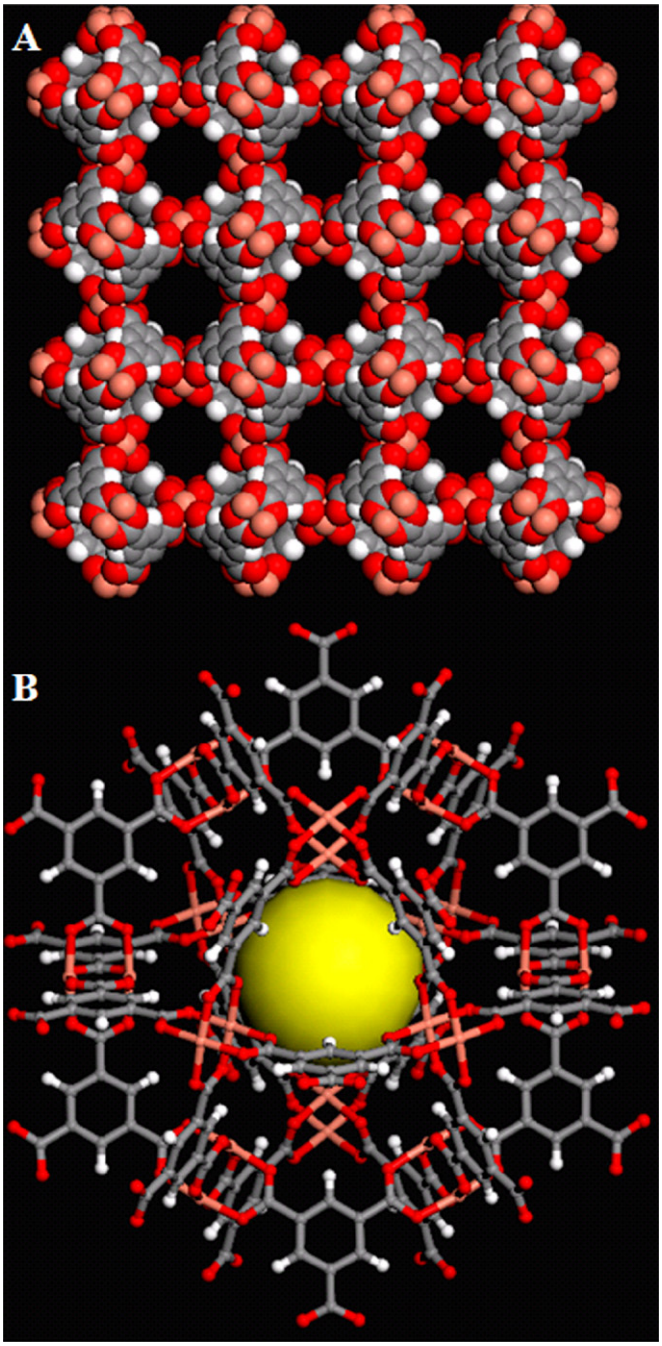
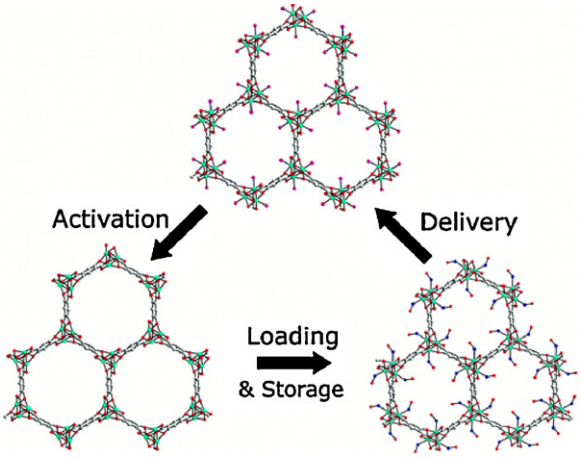


Fig. 7. (A) CPK diagram of HKUST-1 framework. (B) Cubeoctahedron pore of HKUST-1 (a yellow sphere inserted to illustrate the pore cavity). Color key: pink, Cu; red, O; gray, C; white, H.

3.2.1. Adsorption/desorption-type coordination polymers as NO delivery systems

The first example of a coordination polymer as a carrier to deliver NO was reported by Morris and co-workers [115]. Morris and co-workers studied NO adsorption, storage and release in HKUST-1, a copper benzene tricarboxylate porous coordination polymer (Fig. 7) [10]. NO was adsorbed onto dehydrated HKUST-1. At 298 K the adsorption capacity at 1 bar is over 3 mmol/g, which is higher than those of most zeolites and organic polymers. Significant



Scheme 2. Cycle of activation, loading, storage, and delivery that determines the success of a gas-storage material (Co- and Ni-MOF). Color key: cyan, Ni/Co; red, oxygen; gray, carbon; pink, oxygen of coordinated water molecules. Hydrogen atoms and noncoordinated guest molecules have been omitted for clarity. Reprinted from Ref. [116]. Copyright 2008, with permission from American Chemical Society.

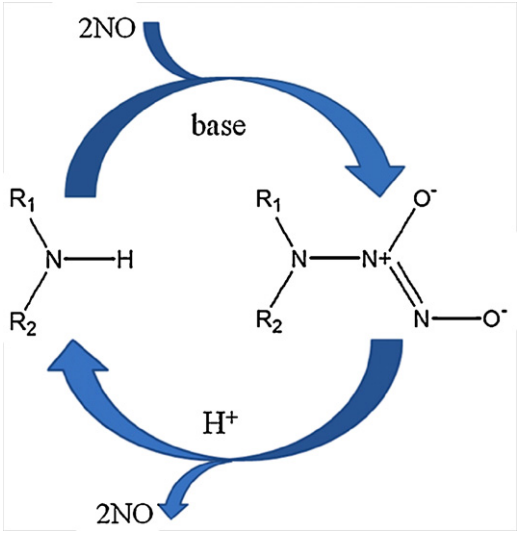


Fig. 8. The formation of diazeniumdiolate group and the NO release mechanism.

isotherm hysteresis was observed, indicating strong irreversible adsorption of some of the NO molecules on coordinatively unsaturated metal sites (CUS). Only a small fraction of the physisorbed NO was desorbed during their experiments. There was 2.21 mmol/g of NO that cannot be desorbed when NO pressure was reduced to almost zero, which approximately corresponds to 1:1 molar ratio between NO and dicopper tetracarboxylate secondary building units (SBU). NO release was carried out by exposing NO-loaded HKUST-1 to a flow of wet gas at a controlled relative humidity. Water acts as a nucleophile to trigger the NO release. However, the total released NO amount is only 0.002 mmol/g, which is 3 orders of magnitude less than the adsorbed amount – 3 mmol/g. NO-loaded HKUST-1 showed promising antithrombotic properties. One drawback of NO-loaded HKUST-1 is the fact that HKUST-1 is unstable in biological solutions, which could give rise to toxicological issues.

In a more recent study by Morris and co-workers [116], two coordination polymers, CPO-27–Co and CPO-27–Ni [117–120], showed exceptional performance over the whole adsorption-storage-delivery cycle for NO (Scheme 2). Both activated CPO-27 coordination polymers can adsorb ~7.0 mmol NO/g of solids. Considerable isotherm hysteresis was also observed in the study. Following the same method as in Ref. [115], NO-loaded CPO-27–Co and NO-loaded CPO-27–Ni released ~7 mmol NO/g of solids, illustrating that the entire amount of adsorbed NO was recoverable. CPO-27–Co/Ni can deliver ~7 mmol NO/g of solids upon exposure to moisture, which is 3 orders of magnitude greater than that by HKUST-1 and 7 times greater than that by the best zeolites [116]. It is not surprising that metals could affect the release kinetics due to the difference in metal–NO binding interactions. For instance, CPO-27–Ni released NO faster than CPO-27–Co due to the relatively weaker interactions between NO and Ni. NO release rate also depends on the release medium. The half life of NO delivery from CPO-27 coordination polymers was reduced from several hours in flowing wet gas to approximately 10 min in PBS buffer. Another advantage of using coordination polymers to delivery NO is that only pure NO was delivered in this study. It is true that Co and Ni are not toxicologically ideal. However, considering the exceptionally high NO adsorption/release performance of CPO-27–Co/Ni coordination polymers, there is a good chance for these materials to be effectively administered *in vivo* within Tolerable Upper Intake levels of metals [79]. Morris also pointed out that there was a possibility to separate metals from human tissue by a gas-permeable membrane to minimize the issue of metal toxicity.

Rigid HKUST-1 (Cu) and CPO-27 (Ni/Co) coordination polymers have comparable (of the same order of magnitude) NO adsorption capacities but their release properties vary significantly (difference of 3 orders of magnitude). The difference of the binding energy between metal and NO is the reason. Cu–NO bond enthalpies are as high as ~90 kJ/mol. Therefore, the strong Cu–NO binding interactions prevent NO-loaded HKUST-1 releasing most of the chemisorbed NO. It is interesting that, in some cases, one can take the advantage of strong binding of Cu–NO in exploring NO delivery systems. Morris and co-workers demonstrated one example of using a flexible coordination polymer, Cu-SIP-3, to adsorb and release NO [121]. This coordination polymer experienced structure transformation stimulated by dehydration. The dehydrated Cu-SIP-3 is essentially non-porous, and below 10 bar no significant uptake of N_2, H_2, CO_2, CO, N_2O or CH_4 by the material was observed in this study. However, above 275 mbar Cu-SIP-3 started to adsorb NO and reached the loading capacity of ~1.1 mmol NO/g of coordination polymer at 1 bar. Upon exposure to water vapor, NO-loaded Cu-SIP-3 released NO completely and was converted to the original hydrated form. This observation also suggests that not only the metal–NO binding energy but also structures and chemical compositions of coordination polymers can produce important effects on the NO release behavior.

3.2.2. *Postsynthesis-modified coordination polymers as NO delivery systems*

An alternative approach to deliver NO by postsynthetic transformations of coordination polymers has also been explored. Rosseinsky and co-workers reported a two-step postsynthetic transformation of HKUST-1 to generate diazeniumdiolates inside of the coordination polymer pores [122]. The diazeniumdiolate functional group formed by strong binding of NO and secondary amine sites is regarded as a “masked” version of NO because NO release from diazeniumdiolate can be efficiently triggered by water (Fig. 8) [108,123]. In this contribution, HKUST-1 was first modified by a non-covalent coordination reaction with 4-(methylanino)-pyridine (4-map). The coordinated 4-map oriented into the larger cubeoctahedron pores. By exposing the modified HKUST-1 to NO (2 bar, 72 h, 293 K), the second step, covalent modifications, took place to form diazeniumdiolates. After removal of physisorbed NO, a crystalline material with the formula of $[Cu_3(btc)_2(4\text{-map})_{1.8}(NO)_{0.7}]_n$ was formed. $[Cu_3(btc)_2(4\text{-map})_{1.8}(NO)_{0.7}]_n$ was resistant to NO

Table 3
A summary of drug delivery behaviors of coordination polymers.

Coordination polymer	Drug	Delivery type	Drug loading (drug/carrier)	Drug release	Conditions	Reference
MIL-100 (Cr)	Ibuprofen	Adsorption/desorption	35%, w/w	Zero-order (for the 1st 2 h) 100% released in 3 days	SBF/37 °C	[49]
MIL-101 (Cr)	Ibuprofen	Adsorption/desorption	140%, w/w	"Higuchi" (for the 1st 8 h) 100% released in 6 days	SBF/37 °C	[49]
MIL-53 (Cr)	Ibuprofen	Adsorption/desorption	20%, w/w	Zero-order 100% released in 3 weeks	SBF/37 °C	[98]
MIL-53 (Fe)	Ibuprofen	Adsorption/desorption	20%, w/w	Zero-order 100% released in 3 weeks	SBF/37 °C	[98]
Bio-MOF-1 (Zn)	Procainamide	Adsorption/desorption (Cation-triggered)	22%, w/w	70% released in 20 h, 100% released in 3 days	PBS/RT	[100]
BIOMIL1 (Fe)	Vitamin B3	Degradation	71.5%, w/w	100% released in 1 h	PBS/37 °C	[101]

loss upon prolonged exposure to vacuum and was stable in an inert atmosphere. Upon exposure to an ambient atmosphere, this material released NO gradually over 5 days. When suspended in deionized water, NO was completely released within 18 h. However, this material leached significant amounts of 4-map during the NO release in water, so its usefulness is limited somehow.

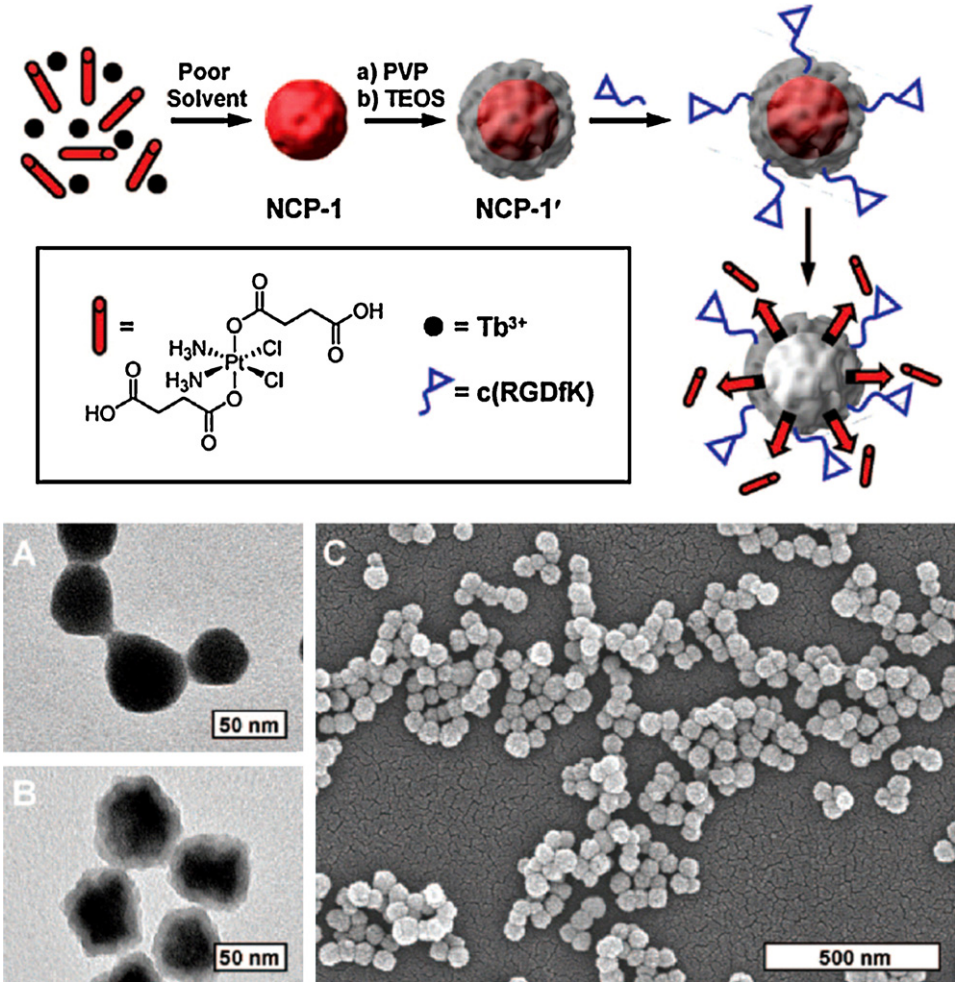
Instead of generating diazeniumdiolates on the coordinated 4-map ligand, Cohen and co-workers functionalized two coordination polymers [124], IRMOF-3 [125] and UMCM-1-NH_2 [126], in which the ligand contains pendant amines. TGA spectra suggested 44% and 88% of the amines have been modified in IRMOF-3 and UMCM-1-NH_2, respectively. NO release studies were performed in PBS (pH = 7.4). These two coordination polymers decomposed rapidly in ~5 min. Functionalized IRMOF-3 released 0.51 mmol NO/g of material, and functionalized UMCM-1 released 0.10 mmol NO/g of material. Cohen's work showed that amine-containing coordination polymers can be covalently functionalized as NO delivery materials.

3.3. Summary and outlook

Drug delivery and NO delivery behavior of bulk coordination polymers are summarized in Tables 3 and 4, respectively. With regards to the *in vitro* drug delivery using coordination polymers as carriers, two types of drug delivery mechanisms are observed: adsorption/desorption of drug molecules and degradation of coordination polymers in which drug acts as the ligand. In particular, the desorption of Procainamide from Bio-MOF-1 was cation-triggered. There are also two approaches for NO delivery utilizing coordination polymers: adsorption/desorption of NO, postsynthesis of coordination polymers by forming diazeniumdiolate (a "masked" version of NO) and the following NO release triggered by water. It is obvious that pore sizes of coordination polymer cavities play an essential role in controlling the drug loading capacity. However, the NO loading capacity in coordination polymers appears to be mainly dependent upon the chemical compositions of coordination polymers, specifically mol% of transition metal or mol% of $-NH_2$, as

Table 4
A summary of NO delivery behaviors of coordination polymers.

Coordination polymer	Delivery type	NO loading (NO/carrier)	NO release	Conditions	Reference
HKUST-1 (Cu)	Adsorption/desorption	3 mmol/g	0.002 mmol/g (maximum)	Flow of wet gas	[115]
CPO-27-Co	Adsorption/desorption	7 mmol/g	7 mmol/g (maximum)	Flow of wet gas	[116]
CPO-27-Ni	Adsorption/desorption	7 mmol/g	7 mmol/g (maximum)	Flow of wet gas	[116]
Cu-SIP-3	Adsorption/desorption	1.1 mmol/g	1.1 mmol/g (maximum)	Water vapor	[121]
HKUST-1(4-map) (Cu)	Postsynthesis Release triggered by water	70.0%, mol/mol	100% released in 5 days 100% released in 18 h	Ambient atmosphereWater	[122]
IRMOF-3 (Zn)	Postsynthesis Release triggered by water	44%, mol/mol	0.51 mmol/g released in 5 min	PBS	[124]
UMCM-1-NH_2	Postsynthesis Release triggered by water	88%, mol/mol	0.10 mmol/g released in 5 min	PBS	[124]



Scheme 3. Schematic illustration of the drug delivery process utilizing NCP-1. (A) TEM micrograph for as-synthesized NCP-1. (B) TEM and (C) SEM micrographs for NCP-1-b. Reprinted from Ref. [136]. Copyright 2008, with permission from American Chemical Society.

long as the target site of coordination polymer (transition metal or $-NH_2$) is accessible for NO. Similarly, for adsorption/desorption-type coordination polymer delivery systems, small molecule drugs or NO can be either chemisorbed by forming coordination bonds to transition metals or physisorbed into coordination polymers by weaker intermolecular forces.

For coordination polymer drug delivery systems, substantial chemical characterizations and computational studies of these materials helpfully facilitate analyzing the drug release kinetics. In order to make unbiased comparisons, we should only choose these coordination polymers carrying the same drug, and the drug release experiments should be carried out under the same conditions. As can be seen in Table 3, MIL-100, MIL-101 and MIL-53 can be selected for comparison purposes. Although the binding energy of Ibuprofen to MIL-53 (57 kJ/mol) is lower than that of Ibuprofen to MIL-101 (73.17 kJ/mol), the release rate of MIL-53 filled with Ibuprofen was much slower. Their drug release rates seem to be contradictory to the order of the drug-matrix binding energy. It might be a plausible hypothesis that MIL-101 has a faster release rate because of its larger pore size. However, such an argument does not explain why MIL-100 (with smaller pore size) releases Ibuprofen at a faster rate compared to both MIL-35 and MIL-101. This could be attributed to the ionization state of Ibuprofen. As in MIL-100/IBU and MIL-101/IBU, two classes of deprotonated Ibuprofen molecules (coordinated and weakly interacted) exist in the cages, resulting in a "two-stage" release profile. However, in MIL-53/IBU, only neutral Ibuprofen molecules exist in the matrix by forming

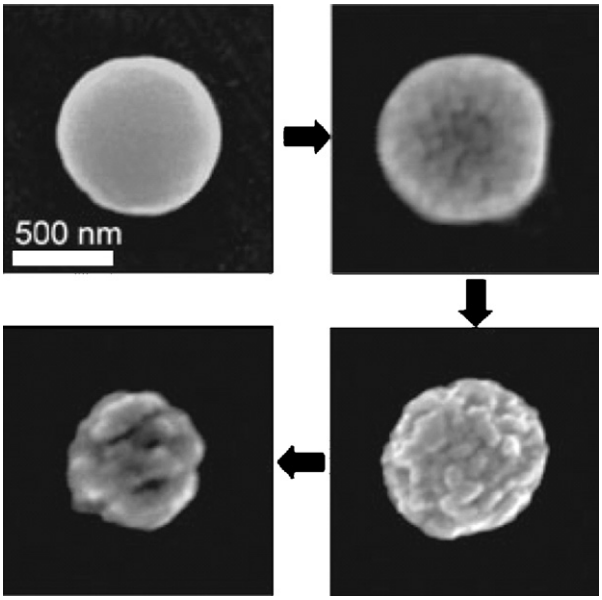
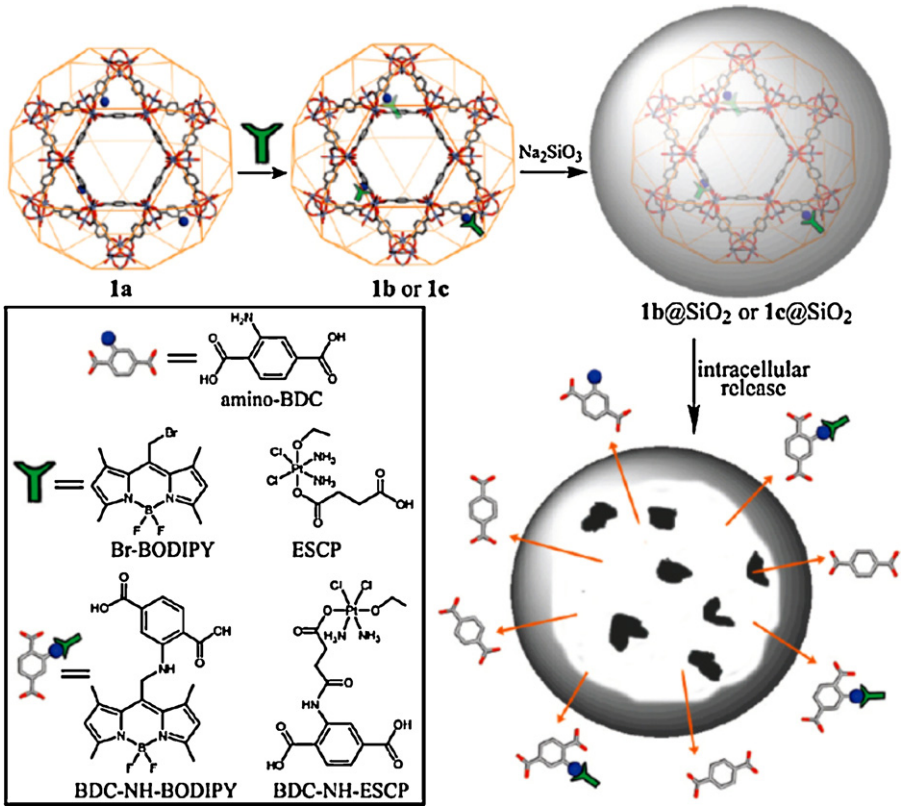


Fig. 9. SEM micrographs of DOX/Zn(bix) spheres taken at 1, 4, 8, and 24 h, showing representative degradation in pH 7.4 PBS at 37 °C. Reprinted from Ref. [144]. Copyright 2010, with permission from the Royal Society of Chemistry.



Scheme 4. Schematic illustration of the drug delivery process of NMOF **1a** via postsynthesis. Reprinted from Ref. [137]. Copyright 2009, with permission from American Chemical Society.

strong hydrogen bonds, which showed a zero order release profile. Based on the current data, it is reasonable to conclude that not only the binding energy but also subtle changes in molecular interaction types between drug molecules and the host matrix can lead to various drug release kinetics.

Rosi's work suggested drug release kinetics can change drastically in different release media, especially for API in salt forms [100]. Che and co-workers have also demonstrated the formation and cleavage of coordination bonds are sensitive to pH variations [127]. It should be noted herein that *in vitro* drug release experiments are performed to simulate real *in vivo* drug release behavior, so the selected dissolution medium should be representative of the biological fluid in terms of pH, ionic strength, surfactant, etc. In addition, the desired drug administration pattern (for example, gastric release, enteric release, etc.) and the solubility of drug should also be taken into consideration when evaluating drug release profiles.

With regards to coordination polymer NO delivery systems, in some cases, the adsorbed NO cannot be completely released due to the strong transition metal-NO coordination bond. This impairs the recyclability and efficiency of NO carrier materials. A solution is to use coordination polymers in which the transition metals bind less tightly with NO. Morris's work also suggested NO release behavior is sensitive to structure and chemical composition. On the other hand, pioneering contributions of delivering NO via postsynthesis by Rosseinsky and Cohen implied the large possibility of using amine-containing coordination polymers as NO delivery materials.

Coordination polymers have shown superior drug loading capacities and, in some cases, well-controlled release kinetics. It is true that early reported Cr-containing coordination polymers may not be suitable for biomedical applications due to the toxicity of Cr, however, the encouraging results of these *proof-of-principle* materials led to following studies of coordination polymers with much less toxic metals such as Zn and Fe. Much progress has been made to date. Besides the reported advantages of coordination polymers in drug delivery such as high drug loading capacity and well-controlled drug release kinetics, there are also many other aspects of coordination polymers that deserve to be studied in the future. For instance, β-cyclodextrin is widely used in the pharmaceutical industry for many advantages resulted from its open porous structure (a height of ~0.79 nm and an inside diameter of ~0.74 nm) and lipophilic interior: inhibit drug crystallization; improve patient compliance (taste masking); simplify handling (absorb oils/liquid); prevent ingredient interactions [128]. Many coordination polymers have comparable or even larger pore size and cavity volume than β-cyclodextrin, and possess lipophilic interiors composed of organic ligands as well. Therefore, coordination polymers may very possibly have these similar positive attributes as cyclodextrins in drug product developments.

4. Nanoscale and microscale coordination polymers in drug delivery

Nanoscale and microscale DDSs, such as polymers, liposomes, and dendrimers, have been extensively studied over the past few decades [129–132]. Benefiting from their small sizes, nanoscale and microscale DDSs often exhibit the following positive aspects [133–135] in comparison with other DDSs: (1) enhanced drug solubility; (2) efficient crossing of biological membranes; (3) amelioration in tissue tolerance; and (4) improved cellular uptake and transport. The concept of nanoscale and microscale DDSs is also widely acceptable in the pharmaceutical industry nowadays. Many drugs are formulated to nanoscale or microscale particles either in their pure forms or prepared together with some key excipients to obtain better bioavailability. A number of advanced formulation techniques (spray drying, micro fluidization, nano milling, etc.) to

Table 5
Structure description, particle size, drug loading (wt%) and entrapment efficiency (below the drug loading values in parentheses, wt%) in several porous iron(III) carboxylate nanoparticles. Reprinted by permission from Macmillan Publishers Ltd: Nature Materials, Ref. [138], Copyright 2010.

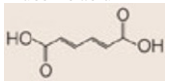
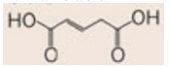
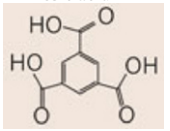
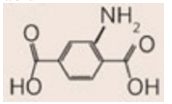
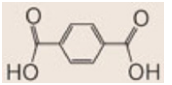
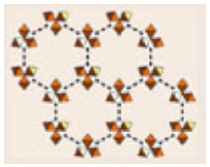
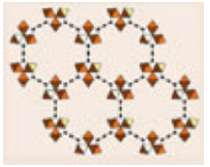
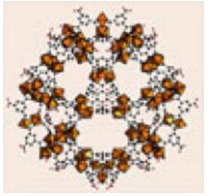
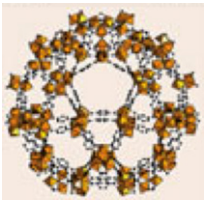
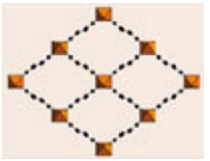
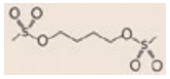
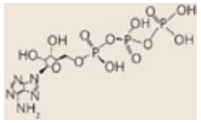
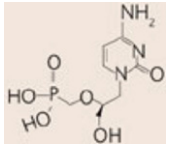
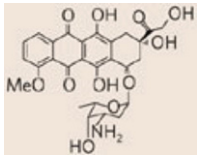
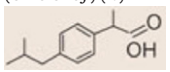
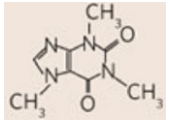
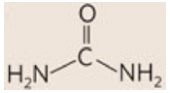
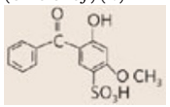
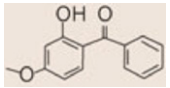
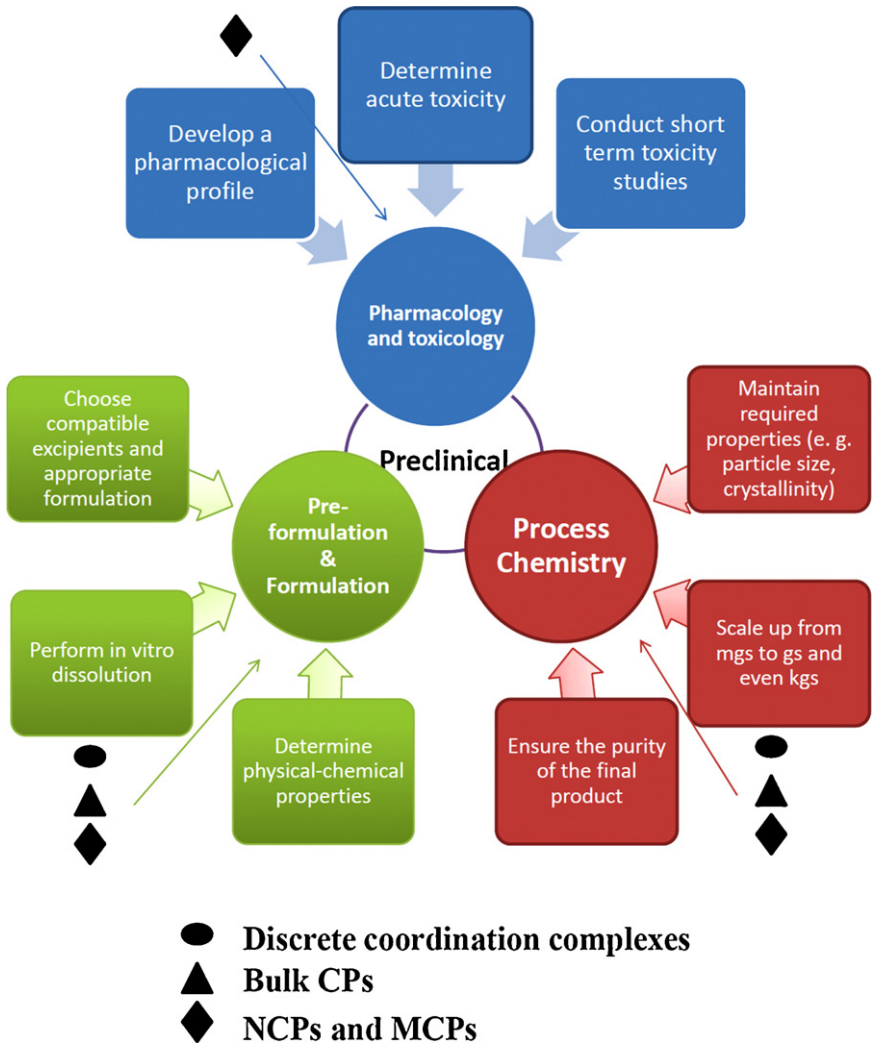
		MIL-89	MIL-88A	MIL-100	MIL-101 _NH2	MIL-53
Organic linker		Muconic acid 	Fumaric acid 	Trimesic acid 	Amino terephthalic acid 	Terephthalic acid 
Crystalline structure						
Flexibility		Yes	Yes	No	No	Yes
Pore size (Å)		11	6	25 (5.6) 29 (8.6)	29 (12) 34 (16)	8.6
Particle size (nm)		50–100	150[a]	200	120	350[a]
Bu loading (efficiency) (%) 	13.4 × 3.5 amphiphilic	9.8 (4.2)	8.0 (3.3)	25.5 (31.9)	–	14.3 (17.9)
AZT-TP loading (efficiency) (%) 	11.9 × 9.1 hydrophilic	–	0.60 (6.4)	21.2 (85.5)	42.0 (90.4)	0.24 (2.8)
CDV loading (efficiency) (%) 	10.8 × 7.7 hydrophilic	14 (81)	2.6 (12)	16.1 (46.2)	41.9 (68.1)	–
Doxorubicin loading (efficiency) (%) 	15.3 × 11.9 hydrophobic	–	–	9.1 (11.2)	–	–

Table 5 (*Continued*)

		MIL-89	MIL-88A	MIL-100	MIL-101 _NH2	MIL-53
Ibuprofen loading (efficiency) (%) 	10 × 5 hydrophobic	–	–	33 (11.0)	–	22 (7.3)
Caffeine loading (efficiency)(%) 	6.1 × 7.6 amphiphilic	–	–	24.2 (16.5)	–	23.1 (15.7)
Urea loading (efficiency) (%) 	4.1 × 3.1 hydrophilic	–	–	69.2 (2.1)	–	63.5 (1.9)
Benzophenone 4 loading (efficiency) (%) 	12.0 × 7.2 hydrophilic	–	–	15.2 (22.8)	–	5 (7.5)
Benzophenone 3 loading (efficiency) (%) 	12.1 × 5.6 hydrophobic	–	–	(74.0)	–	–

[a] Bimodal distribution of sizes, with micrometric particles.



Scheme 5. Schematic illustration of major activities at the stage of preclinical development of a drug.

manufacture nanoscale or microscale drug products are commercially available. Inspired by the encouraging drug delivery results of bulk coordination polymers and by the proven positive advantages of other types of nano/micro DDSs, researchers have also taken initiative to explore nanoscale and microscale coordination polymers (NCPs and MCPs) in drug delivery.

4.1. Nanoscale coordination polymers as drug delivery systems

In 2008, Lin and co-workers reported the first example of utilizing nanoscale coordination polymers (NCPs) in drug delivery [136]. The $[Tb_2(DSCP)_3(H_2O)_{12}]_n$ (DSCP, disuccinatocisplatin) NCP, NCP-1, was prepared by the addition of an anti-solvent into the precursor solution. The drug (DSCP) content in NCP-1 is 73.7% w/w by its formula. Dynamic light scattering gave a diameter of 58.3 ± 11.3 nm for the as-synthesized spherical NCP-1 particles (Scheme 3). Lin encapsulated the amorphous NCP-1 particles by coating amorphous silica to improve the stability of NCP particles in the aqueous phase. The drug release mechanism can be shown schematically in Scheme 3. Two types of coated NCP particles were obtained: NCP-1′-a (shell thickness ~2 nm) and NCP-1′-b (shell thickness ~7 nm). The drug release experiments were performed in HEPES buffer (pH = 7.4) at 37 °C. Release of DSCP was accompanied by the degradation of NCP-1. The release rate was also modulated by the thickness of the silica shell. For example, NCP-1 particles had a half-life of ~1 h in the buffer, while NCP-1′-a and NCP-1′-b gave a half life of ~5.5 h and ~9 h respectively. The controlled drug release by coating NCP particles with silica can be compared with multiparticulate systems in the pharmaceutical industry, the principle of which is similar.

Lin and co-workers also reported a new strategy of delivering an imaging contrast agent and an anticancer drug by postsynthetic modifications of NCP [137], shown in Scheme 4. In order to allow for postsynthetic modifications, the authors incorporated 2-aminoterephthalic acid (NH_2-BDC) besides terephthalic acid (BDC). Two Fe containing NCPs were prepared: NMOF **1a** with the MIL-101 structure and NMOF 2 with the MIL-88B structure, varying according to the amount of NH_2-BDC in the feed. NMOF **1a** (17.4 mol% NH_2-BDC) was chosen as the starting material for its large pore size. NMOF **1a** particles reacted with 1,3,5,7-tetramethyl-4,4-difluoro-8-bromomethyl-4-bora-3a,4a-diaza-s-indacene (Br-BODIPY) forming **1b** particles. NMOF **1a** particles also reacted with the ethoxysuccinato-cisplatin prodrug [ESCP], *c,c,t*-$[PtCl_2(NH_3)_2(OEt)(O_2CCH_2CH_2CO_2H)]$, forming **1c** particles. XRPD patterns showed that **1b** and **1c** retained the MIL-101 structure. The overall drug loading of ESCP in **1c** particles were 12.8% w/w. Na_2SiO_3 was used as the silica source to coat **1b** and **1c** particles. Silica coated **1c** particles were tested for its drug release profiles. The drug release experiments were performed in PBS buffer at 37 °C. The coordination polymer network

Table 6
A summary of drug delivery behaviors of NCPs and MCPs.

Coordination polymer	Drug	Delivery type	Drug loading (drug/carrier)	Drug release	Conditions	Reference
NCP-1′-a (Tb)	DSCP	Degradation	73.7%, w/w (in NCP-1)	Half life ~5.5 h	HEPES/37 °C	[136]
NCP-1′-b (Tb)				Half life ~9 h		
NCP **1c** (Pt)	ESCP	Postsynthesis Degradation	12.8%, w/w	Half life ~14 h	PBS/37 °C	[137]
MIL NCPs (Fe)	[a]	Adsorption/desorption	[a]	[a]	PBS/37 °C	[138]
[Zn(bix)] colloids (Zn)	DOX SN-38	Encapsulation Desorption/diffusion Erosion	21% of the initial drug concentration	80% released in 8 h, 100% released in 2 days	PBS/37 °C	[144]

[a] Refer to Table 5 for details.

degraded during the drug release process. The release of BDC-NH-ESCP from **1c**@silica gave a half life of ~14 h. Complete drug release was achieved within 80 h. Postsynthesized **1c** @ Si also showed promising anticancer efficacy.

Very recently Horcajada and co-workers reported a comprehensive study of nanoscale porous coordination polymers as the potential platform for drug delivery [138]. A class of non-toxic MIL(Fe) coordination polymers were prepared as nanoparticles. In animal studies, no significant toxic effects were observed for these NCPs up to 10 days after administration. Their efficiency as DDSs was tested with a series of drugs (Table 5) varied according to their molecule sizes and lipophilicity. MIL nanoparticles showed exceptionally higher drug loading capacities compared to the usual nanocarriers [139]. For example, busulfan (Bu), a widely used anticancer drug, had a loading of 25%, w/w in MIL-100(Fe) NCP, which is significantly higher than that of organic DDSs such as polymer nanoparticles (5 times higher) [140] and liposomes (60 times higher) [141,142]. The drug release of AZT-TP, CDV and doxo using MIL-100(Fe) nanoparticles in PBS at 37 °C exhibited no "burst effect". However, drug delivery trials of MIL nanoparticles with smaller pore size than the drug molecule, for instance - release of AZT-TP using MIL-53(Fe) nanoparticles, had low drug loading and exhibited "burst" release kinetics. This is attributed to the fact that the drug was only physisorbed onto the external surface of nanoparticles and not within the pores. Anti-HIV activities of AZT-TP loaded NCPs were also proven. Moreover, MIL-100(Fe) nanoparticles had a reasonable stability in PBS: after the complete release of AZT-TP in 3 days, only approximately 10% of MIL-100(Fe) NCP was degraded. Therefore, Horcajada and co-workers suggested the drug delivery process using MIL NCPs was governed mainly by diffusion from the pore and/or drug-matrix interactions and not by the NCP degradation. In addition, these nanoscale MIL coordination polymers also showed potentials as contrast agents. Indeed, this work has demonstrated many advantages of porous Fe-carboxylate NCPs for biomedical applications, particularly their great potentials for the treatment of life threatening diseases, for example, cancer and HIV.

4.2. Coordination polymer colloids as drug delivery systems

Maspoch and co-workers first used coordination polymer colloids for guest encapsulation [143]. In this contribution, coordination polymer colloids were prepared following a one-step procedure. A water solution of $Zn(NO_3)_2$ was added to an ethanol solution of 1,4-Bis(imidazol-1-ylmethyl)benzene (bix) and desired species, with sonication or vigorous stirring. The formation of colloids and the encapsulation of desired species were concomitant. Due to the flexible conformation of bix, the $[Zn(bix)(NO_3)_2]$ coordination polymer colloids are amorphous (confirmed by XRPD). By controlling reaction conditions, uniform colloidal spheres could be prepared with diameters in the range of 100–1500 nm. Maspoch demonstrated that coordination polymer colloids can be applied successfully to encapsulate magnetic nanoparticles, quantum dots and organic dyes.

Later Maspoch and co-workers reported coordination polymer colloids in drug delivery as a follow-up work [144]. Four prototypes of anticancer drugs, Doxorubicin (DOX), SN-38, camptothecin (CPT), and daunomycin (DAU) were investigated in this work. The drug encapsulation efficiency was up to 21% of the initial drug concentration. The fluorescence emission spectra of the colloids matched those of free drugs. The drug release of DOX/Colloid and SN-38/Colloid were performed in PBS (pH = 7.4) at 37 °C in a dialysis bag (cut-off molecular weight: 3500). Zn(bix) colloidal spheres showed a fast release of ~80% of drug within 8 h, followed by a sustained release of the remainder over the next 2 days. The first stage of fast release should be attributed to the combinatory process of desorption and diffusion. The second stage of sustained release reflected the slow release of drug molecules encapsulated in the core, which was limited by the erosion speed of colloids in the buffer. The erosion of colloidal spheres (Fig. 9) was proven by SEM and DLS. The anticancer efficacies of as-prepared drug loaded colloids *in vitro* were also demonstrated in this work.

4.3. Summary and outlook

The drug delivery behavior of nanoscale and microscale coordination polymers is summarized in Table 6. There are four routes for the drug uptake into nanoscale and microscale coordination polymers: (1) adsorption; (2) acting as ligands; (3) postsynthesis; and (4) concomitant encapsulations of drugs in solution by forming colloids. There are also four types of release mechanisms for drug-loaded nanoscale and microscale coordination polymers: (1) desorption; (2) degradation; (3) diffusion; and (4) erosion. In some cases, multiple drug release mechanisms take place for one drug delivery system; however, one type of mechanism may dominate the drug release kinetics during certain period of time.

Compared to bulk coordination polymers, the drug release from nanoscale and microscale coordination polymer DDSs is shortened from days and weeks to several hours. The significant difference of drug release rates is mainly attributed to the difference in particle size. The enhancement of the drug release rate is important in practice because a drug dosage can hardly stay in a patient's body for days and weeks before its degradation and excretion. The range from a few hours to 24 h is normally a more reasonable time scheme for controlled drug release *in vivo*. The use of nanoparticle-stabilizers such as Polyvinyl pyrrolidone (PVP), amorphous Si and Polyethylene glycol (PEG) in NCPs is also noteworthy as these stabilizers are also commonly used pharmaceutical excipients for dosage formulation developments [145]. Nanoparticle-stabilizers can not only protect the nanoparticles from aggregation but also control the drug release rate by adjusting the thickness of coated stabilizers.

In summary, nanoscale and microscale coordination polymers have demonstrated their unique positive advantages in drug delivery, and a variety of drug uptake and release routes have been explored. Particularly Fe-carboxylate NCPs have shown the most promising results in terms of non-toxicity, well-controlled drug release behavior and stability. Routes of administration should also be taken into account when developing NCPs/MCPs as novel drug delivery carriers. For instance, drug loaded NCPs were proposed as injection formulations in Horcajada and co-workers' contribution. The stability of such materials during the sterilization process, which often involves very harsh conditions such as high temperature steam and radiation [146], must be addressed before these NCPs hit the clinical trials. Future research on drug loaded nanoscale and microscale coordination polymers can be dedicated to long term stability of drug loaded NCPs/MCPs at ambient and accelerated conditions, compatibility of NCPs/MCPs with pharmaceutical excipients, and processability of these materials in drug manufacturing.

5. Conclusions

In this review, we have summarized recent work from our group and others. From the foregoing discussions, it is fairly clear that the use of coordination complexes in drug delivery has received growing attention to date. While the use of coordination complexes in drug delivery is still in its infancy, many promising results have been reported and progressive research in this field are being undertaken. Indeed, recent advances of coordination complexes in drug delivery have already demonstrated their great potentials at the stage of preclinical drug development. Scheme 5 demonstrates major activities during the preclinical development of a drug, where APIs and drug-delivery agents are both involved. Most studies of discrete coordination complexes and coordination polymers covered in this review have related to some areas in process chemistry (e.g., crystallinity and purity), pre-formulation (e.g., characterizations of physical–chemical properties) and formulation (e.g., the use of pharmaceutical excipients with NCPs). Only the research of NCP drug delivery systems has touched upon the area of pharmacology and toxicology.

The ultimate goal for coordination complex-based drug delivery systems is to use such agents in real pharmaceutical applications. An initial step to utilize novel drug delivery systems in drug development is to perform careful evaluation at the preclinical stage. As can be seen in Scheme 5, discrete coordination complexes and coordination polymers have already shown their advantages and/or unique properties in some areas of preclinical developments: (1) discrete mixed-ligand coordination complexes can be used to rationally modify physical–chemical properties of API; (2) coordination polymer DDSs have exhibited their well-defined drug release behavior and exceptionally high drug loading capacities; (3) several pharmaceutical excipients have been used as stabilizers to coat drug-loaded NCPs; (4) the preparation of crystalline coordination complexes usually does not require further purification; and (5) some NCPs have been proven to be non-toxic *in vivo* in animal studies. As Morris and Serre pointed out, "this field of research, which has emerged only very recently, has focused on the use of selected MOFs for a few given applications. [147]", there is still a lot of work to do for fulfillment of the opening in the preclinical development. We may foresee the following activities to be realized in the future: (1) systematic pharmacological and toxicological evaluations of coordination complex DDSs; (2) studies of (discrete or polymeric) coordination complexes in process chemistry, e.g., control of NCP particle size, scaled-up production of coordination complexes; (3) formulation and prototype development utilizing API, coordination complex DDSs and other pharmaceutical excipients, e.g., compatibility, prototype stability, processability in manufacturing.

In conclusion, the use of discrete coordination complexes and coordination polymers in drug delivery is at a very early stage. However, there has been significant progress in the use of coordination complexes in drug delivery revealing their unique advantages over many other drug delivery systems, and nowadays many researchers are engaged in this vast but almost untouched field. Encouraged by these promising results, we believe that the future for discrete and polymeric coordination complexes in drug delivery is bright. Meanwhile, in the drug development cycle, the development of novel drug delivery systems utilizing discrete coordination complexes and (bulk or nanoscale/microscale) coordination polymers also leads to conceptual and practical challenges awaiting researchers to conquer, some of which have been proposed in this review.

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.ccr.2011.01.031.

References

[1] D. Braga, F. Grepioni, L. Maini, R. Brescello, L. Cotarca, Crystengcomm 10 (2008) 469.
[2] S. Kitagawa, R. Kitaura, S. Noro, Angew. Chem. Int. Ed. Engl. 43 (2004) 2334.
[3] M. Eddaoudi, D.B. Moler, H.L. Li, B.L. Chen, T.M. Reineke, M. O'Keeffe, O.M. Yaghi, Acc. Chem. Res. 34 (2001) 319.
[4] L.K. Johnson, C.M. Killian, M. Brookhart, J. Am. Chem. Soc. 117 (1995) 6414.
[5] O.R. Evans, W.B. Lin, Acc. Chem. Res. 35 (2002) 511.
[6] B.J. Holliday, C.A. Mirkin, Angew. Chem. Int. Ed. Engl. 40 (2001) 2022.
[7] S. Hasegawa, S. Horike, R. Matsuda, S. Furukawa, K. Mochizuki, Y. Kinoshita, S. Kitagawa, J. Am. Chem. Soc. 129 (2007) 2607.
[8] E. Coronado, J.R. Galan-Mascaros, C.J. Gomez-Garcia, V. Laukhin, Nature 408 (2000) 447.
[9] R.J. Hill, D.L. Long, P. Hubberstey, M. Schroder, N.R. Champness, J. Solid State Chem. 178 (2005) 2414.
[10] S.S.Y. Chui, S.M.F. Lo, J.P.H. Charmant, A.G. Orpen, I.D. Williams, Science 283 (1999) 1148.
[11] O.M. Yaghi, M. O'Keeffe, N.W. Ockwig, H.K. Chae, M. Eddaoudi, J. Kim, Nature 423 (2003) 705.
[12] S. van Zutphen, J. Reedijk, Coord. Chem. Rev. 249 (2005) 2845.
[13] C.W. Schwietert, J.P. McCue, Coord. Chem. Rev. 184 (1999) 67.
[14] J.C.G. Bunzli, Acc. Chem. Res. 39 (2006) 53.
[15] C. Marzano, M. Pellei, F. Tisato, C. Santini, Anticancer Agents Med. Chem. 9 (2009) 185.
[16] L.R. Kelland, Crit. Rev. Oncol. Hematol. 15 (1993) 191.
[17] B.P. Esposito, R. Najjar, Coord. Chem. Rev. 232 (2002) 137.
[18] V.W.W. Yam, K.K.W. Lo, Coord. Chem. Rev. 184 (1999) 157.
[19] T.J. Wadas, E.H. Wong, G.R. Weisman, C.J. Anderson, Curr. Pharm. Des. 13 (2007) 3.
[20] W.J. Rieter, K.M.L. Taylor, H.Y. An, W.L. Lin, W.B. Lin, J. Am. Chem. Soc. 128 (2006) 9024.
[21] G.L. Amidon, H. Lennernas, V.P. Shah, J.R. Crison, Pharm. Res. 12 (1995) 413.
[22] D.X. Sun, L.X. Yu, M.A. Hussain, D.A. Wall, R.L. Smith, G.L. Amidon, Curr. Opin. Drug. Discov. Dev. 7 (2004) 75.
[23] Y.Y. Chiu, K. Higaki, B.L. Neudeck, J.L. Barnett, L.S. Welage, G.L. Amidon, Pharm. Res. 20 (2003) 749.
[24] N.A. Kasim, M. Whitehouse, C. Ramachandran, M. Bermejo, H. Lennernas, A.S. Hussain, H.E. Junginger, S.A. Stavchansky, K.K. Midha, V.P. Shah, G.L. Amidon, Mol. Pharm. 1 (2004) 85.
[25] T. Takagi, C. Ramachandran, M. Bermejo, S. Yamashita, L.X. Yu, G.L. Amidon, Mol. Pharm. 3 (2006) 631.
[26] J. Broadhead, S.K.E. Rouan, C.T. Rhodes, Drug. Dev. Ind. Pharm. 18 (1992) 1169.
[27] N. Rasenack, B.W. Muller, Pharm. Dev. Technol. 9 (2004) 1.
[28] C.W. Pouton, Eur. J. Pharm. Sci. 11 (2000) S93.
[29] T. Loftsson, M.E. Brewster, J. Pharm. Sci. 85 (1996) 1017.
[30] Z. Ma, B. Moulton, Cryst. Growth Des. 7 (2007) 196.
[31] Z. Ma, B. Moulton, Mol. Pharmaceutics. 4 (2007) 373.
[32] Z. Ma, R. Hopson, C. Cai, S. Han, B. Moulton, Cryst. Growth Des. 10 (2010) 2376.
[33] J. Siepmann, N.A. Peppas, Adv. Drug Deliv. Rev. 48 (2001) 139.
[34] A. Hoffman, M. Donbrow, S.T. Gross, S. Benita, R. Bahat, Int. J. Pharm. 29 (1986) 195.
[35] M. Rodriguez, J.L. Vila-Jato, D. Torres, J. Control. Release 55 (1998) 67.
[36] P. Costa, J. Manuel, S. Lobo, Eur. J. Pharm. Sci. 13 (2001) 123.
[37] L.S. Taylor, G. Zografi, Pharm. Res. 14 (1997) 1691.
[38] J. Siepmann, H. Kranz, R. Bodmeier, N.A. Peppas, Pharm. Res. 16 (1999) 1748.
[39] G. Gregoriadis, Trends Biotechnol. 13 (1995) 527.

[40] T. Lian, R.J.Y. Ho, J. Pharm. Sci. 90 (2001) 667.
[41] K.S. Soppimath, T.M. Aminabhavi, A.R. Kulkarni, W.E. Rudzinski, J. Control. Release 70 (2001) 1.
[42] S. Freiberg, X. Zhu, Int. J. Pharm. 282 (2004) 1.
[43] B. Munoz, A. Ramila, J. Perez-Pariente, I. Diaz, M. Vallet-Regi, Chem. Mater. 15 (2003) 500.
[44] P. Horcajada, C. Marquez-Alvarez, A. Ramila, J. Perez-Pariente, M. Vallet-Regi, Solid State Sci. 8 (2006) 1459.
[45] J.H. Yang, Y.S. Han, M. Park, T. Park, S.J. Hwang, J.H. Choy, Chem. Mater. 19 (2007) 2679.
[46] Z. Gu, A.C. Thomas, Z.P. Xu, J.H. Campbell, G.Q. Lu, Chem. Mater. 20 (2008) 3715.
[47] H. Zhang, D.K. Pan, X. Duan, J. Phys. Chem. C.: Nanomater. Interfaces 113 (2009) 12140.
[48] M.R. Lopez-Ramirez, C. Ruano, J.L. Castro, J.F. Arenas, J. Soto, J.C. Otero, J. Phys. Chem. C.: Nanomater. Interfaces 114 (2010) 7666.
[49] P. Horcajada, C. Serre, M. Vallet-Regi, M. Sebban, F. Taulelle, G. Férey, Angew. Chem. Int. Ed. Engl. 45 (2006) 5974.
[50] J.M. Lehn, Angew. Chem. Int. Ed. Engl. 27 (1988) 89.
[51] B. Moulton, M.J. Zaworotko, Chem. Rev. 101 (2001) 1629.
[52] G.R. Desiraju, Angew. Chem. Int. Ed. Engl. 34 (1995) 2311.
[53] D.J. Good, N. Rodriguez-Hornedo, Cryst. Growth Des. 9 (2009) 2252.
[54] J.A. Bis, P. Vishweshwar, D. Weyna, M.J. Zaworotko, Mol. Pharm. 4 (2007) 401.
[55] S.G. Fleischman, S.S. Kuduva, J.A. McMahon, B. Moulton, R.D.B. Walsh, N. Rodriguez-Hornedo, M.J. Zaworotko, Cryst. Growth Des. 3 (2003) 909.
[56] S.L. Childs, P.A. Wood, N. Rodriguez-Hornedo, L.S. Reddy, K.I. Hardcastle, Cryst. Growth Des. 9 (2009) 1869.
[57] M.A. Yu, Y. Chen, N. Zhang, Y. Liu, Org. Biomol. Chem. 8 (2010) 4148.
[58] B. Viossat, G. Morgant, J.R.J. Sorenson, M. Roch-Arveiller, J.C. Daran, F.T. Greenaway, D.N. Huy, Ann. Pharm. Fr. 60 (2002) 102.
[59] D. Kovala-Demertzi, A. Galani, M.A. Demertzis, S. Skoulika, C. Kotoglou, J. Inorg. Biochem. 98 (2004) 358.
[60] G. Tamasi, F. Serinelli, M. Consumi, A. Magnani, M. Casolaro, R. Cini, J. Inorg. Biochem. 102 (2008) 1862.
[61] L.Z. Benet, C. Wu, J.M. Custodio, Bull. Technol. Gattefosse 99 (2006) 9.
[62] C.W. Pouton, Bull. Technol. Gattefosse 98 (2005) 39.
[63] S.H. Yalkowsky, S.C. Valvani, T.J. Roseman, J. Pharm. Sci. 72 (1983) 866.
[64] S. Pinsuwan, A. Li, S.H. Yalkowsky, J. Chem. Eng. Data 40 (1995) 623.
[65] M. Jozan, K. Takacs-Novak, Int. J. Pharm. 159 (1997) 233.
[66] C. Hansch, J.M. Clayton, J. Pharm. Sci. 62 (1973) 1.
[67] A. Leo, C. Hansch, D. Elkins, Chem. Rev. 71 (1971) 525.
[68] Z. Ma, S.B. Han, V.C. Kravtsov, B. Moulton, Inorg. Chim. Acta 363 (2010) 387.
[69] R.B. Silverman, The Organic Chemistry of Drug Design and Drug Action, Academic Press, London, 1992.
[70] Y. Yoshikawa, E. Ueda, K. Kawabe, H. Miyake, H. Sakurai, Y. Kojima, Chem. Lett. (2000) 874.
[71] L. Allouche, A. Marquis, J.M. Lehnl, Chem.: Eur. J. 12 (2006) 7520.
[72] H. Barjat, G.A. Morris, S. Smart, A.G. Swanson, S.C.R. Williams, J. Magn. Reson. B 108 (1995) 170.
[73] E.J. Cabrita, S. Berger, Magn. Reson. Chem. 39 (2001) S142.
[74] K.F. Morris, C.S. Johnson, J. Am. Chem. Soc. 115 (1993) 4291.
[75] E.R. Jamieson, S.J. Lippard, Chem. Rev. 99 (1999) 2467.
[76] P. Ochsenbein, M. Bonin, O. Masson, D. Loyaux, G. Chapuis, K.J. Schenk, Angew. Chem. Int. Ed. Engl. 43 (2004) 2694.
[77] R. Murugavel, R. Korah, Inorg. Chem. 46 (2007) 11048.
[78] R. Uppal, H.P. Israel, C.D. Incarvito, A.M. Valentine, Inorg. Chem. 48 (2009) 10769.
[79] Food & Nutrition Board Standing Committee on the Scientific Evaluation of Dietary Reference, Dietary Reference Intakes: For Vitamin A, Vitamin K, Arsenic, Boron, Chromium, Copper, Iodine, Iron, Manganese, Molybdenum, Nickel, Silicon, Vanadium, and Zinc, Natl Academy Press, Washington, 2002.
[80] T.D. Hamilton, G.S. Papaefstathiou, T. Friscic, D.K. Bucar, L.R. MacGillivray, J. Am. Chem. Soc. 130 (2008) 14366.
[81] H. Furukawa, J. Kim, N.W. Ockwig, M. O'Keeffe, O.M. Yaghi, J. Am. Chem. Soc. 130 (2008) 11650.
[82] H. Abourahma, A.W. Coleman, B. Moulton, B. Rather, P. Shahgaldian, M.J. Zaworotko, Chem. Commun. (2001) 2380.
[83] J.J. Perry, J.A. Perman, M.J. Zaworotko, Chem. Soc. Rev. 38 (2009) 1400.
[84] T. Schroder, R. Brodbeck, M.C. Letzel, A. Mix, B. Schnatwinkel, M. Tonigold, D. Volkmer, J. Mattay, Tetrahedron Lett. 49 (2008) 5939.
[85] M. Tonigold, J. Hitzbleck, S. Bahnmuller, G. Langstein, D. Volkmer, Dalton Trans. (2009) 1363.
[86] S. Han, Design and Synthesis of Crystalline and Amorphous Coordination Materials, PhD thesis. Advised by B. Moulton, Brown University, Providence, 2009, p. 89.
[87] O. Tegus, E. Bruck, K.H.J. Buschow, F.R. de Boer, Nature 415 (2002) 150.
[88] J. Zaanen, G.A. Sawatzky, J.W. Allen, Phys. Rev. Lett. 55 (1985) 418.
[89] J.M.E. Harper, T.H. Geballe, F.J. Disalvo, Phys. Rev.: B Condens. Matter 15 (1977) 2943.
[90] P.D. Sawant, X.Y. Liu, Chem. Mater. 14 (2002) 3793.
[91] B. Jeong, Y.H. Bae, D.S. Lee, S.W. Kim, Nature 388 (1997) 860.
[92] A.K. Cheetham, G. Férey, T. Loiseau, Angew. Chem. Int. Ed. Engl. 38 (1999) 3268.
[93] B. Luisi, Z. Ma, B. Moulton, J. Chem. Crystallogr. 37 (2007) 743.
[94] J. Perles, N. Snejko, M. Iglesias, M.A. Monge, J. Mater. Chem. 19 (2009) 6504.
[95] G. Férey, C. Serre, C. Mellot-Draznieks, F. Millange, S. Surble, J. Dutour, I. Margiolaki, Angew. Chem. Int. Ed. Engl. 43 (2004) 6296.
[96] G. Férey, C. Mellot-Draznieks, C. Serre, F. Millange, J. Dutour, S. Surble, I. Margiolaki, Science 309 (2005) 2040.
[97] R. Babarao, J.W. Jiang, J. Phys. Chem. C.: Nanomater. Interfaces 113 (2009) 18287.
[98] P. Horcajada, C. Serre, G. Maurin, N.A. Ramsahye, F. Balas, M. Vallet-Regi, M. Sebban, F. Taulelle, G. Férey, J. Am. Chem. Soc. 130 (2008) 6774.
[99] S. Bourrelly, P.L. Llewellyn, C. Serre, F. Millange, T. Loiseau, G. Férey, J. Am. Chem. Soc. 127 (2005) 13519.
[100] J.Y. An, S.J. Geib, N.L. Rosi, J. Am. Chem. Soc. 131 (2009) 8376.
[101] S.R. Miller, D. Heurtaux, T. Baati, P. Horcajada, J.M. Greneche, C. Serre, Chem. Commun. 46 (2010) 4526.
[102] S. Moncada, R.M.J. Palmer, E.A. Higgs, Pharmacol. Rev. 43 (1991) 109.
[103] M.C. Frost, M.M. Reynolds, M.E. Meyerhoff, Biomaterials 26 (2005) 1685.
[104] E.M. Hetrick, J.H. Shin, N.A. Stasko, C.B. Johnson, D.A. Wespe, E. Holmuhamedov, M.H. Schoenfisch, Acs. Nano 2 (2008) 235.
[105] M.R. Miller, I.L. Megson, Br. J. Pharmacol. 151 (2007) 305.
[106] P.G. Wang, M. Xian, X.P. Tang, X.J. Wu, Z. Wen, T.W. Cai, A.J. Janczuk, Chem. Rev. 102 (2002) 1091.
[107] D.J. Smith, D. Chakravarthy, S. Pulfer, M.L. Simmons, J.A. Hrabie, M.L. Citro, J.E. Saavedra, K.M. Davies, T.C. Hutsell, D.L. Mooradian, S.R. Hanson, L.K. Keefer, J. Med. Chem. 39 (1996) 1148.
[108] P.G. Parzuchowski, M.C. Frost, M.E. Meyerhoff, J. Am. Chem. Soc. 124 (2002) 12182.
[109] B. Wu, B. Gerlitz, B.W. Grinnell, M.E. Meyerhoff, Biomaterials 28 (2007) 4047.
[110] F. DeRosa, M.R. Kibbe, S.F. Najjar, M.L. Citro, L.K. Keefer, J.A. Hrabie, J. Am. Chem. Soc. 129 (2007) 3786.
[111] H.P. Zhang, G.M. Annich, J. Miskulin, K. Stankiewicz, K. Osterholzer, S.I. Merz, R.H. Bartlett, M.E. Meyerhoff, J. Am. Chem. Soc. 125 (2003) 5015.
[112] P.S. Wheatley, A.R. Butler, M.S. Crane, S. Fox, B. Xiao, A.G. Rossi, I.L. Megson, R.E. Morris, J. Am. Chem. Soc. 128 (2006) 502.
[113] F.T. Tsai, S.J. Chiou, M.C. Tsai, H.W. Huang, M.H. Chiang, W.F. Liaw, Inorg. Chem. 44 (2005) 5872.
[114] J.L.C. Rowsell, E.C. Spencer, J. Eckert, J.A.K. Howard, O.M. Yaghi, Science 309 (2005) 1350.
[115] B. Xiao, P.S. Wheatley, X.B. Zhao, A.J. Fletcher, S. Fox, A.G. Rossi, I.L. Megson, S. Bordiga, L. Regli, K.M. Thomas, R.E. Morris, J. Am. Chem. Soc. 129 (2007) 1203.
[116] A.C. McKinlay, B. Xiao, D.S. Wragg, P.S. Wheatley, I.L. Megson, R.E. Morris, J. Am. Chem. Soc. 130 (2008) 10440.
[117] F. Bonino, S. Chavan, J.G. Vitillo, E. Groppo, G. Agostini, C. Lamberti, P.D.C. Dietzel, C. Prestipino, S. Bordiga, Chem. Mater. 20 (2008) 4957.
[118] P.D.C. Dietzel, Y. Morita, R. Blom, H. Fjellvag, Angew. Chem. Int. Ed. Engl. 44 (2005) 6354.
[119] P.D.C. Dietzel, B. Panella, M. Hirscher, R. Blom, H. Fjellvag, Chem. Commun. (2006) 959.
[120] P.D.C. Dietzel, R.E. Johnsen, R. Blom, H. Fjellvag, Chem.: Eur. J. 14 (2008) 2389.
[121] B. Xiao, P.J. Byrne, P.S. Wheatley, D.S. Wragg, X.B. Zhao, A.J. Fletcher, K.M. Thomas, L. Peters, J.S.O. Evans, J.E. Warren, W.Z. Zhou, R.E. Morris, Nat. Chem. 1 (2009) 289.
[122] M.J. Ingleson, R. Heck, J.A. Gould, M.J. Rosseinsky, Inorg. Chem. 48 (2009) 9986.
[123] J.A. Hrabie, L.K. Keefer, Chem. Rev. 102 (2002) 1135.
[124] J.G. Nguyen, K.K. Tanabe, S.M. Cohen, Crystengcomm 12 (2010) 2335.
[125] M. Eddaoudi, J. Kim, N. Rosi, D. Vodak, J. Wachter, M. O'Keeffe, O.M. Yaghi, Science 295 (2002) 469.
[126] Z.Q. Wang, K.K. Tanabe, S.M. Cohen, Inorg. Chem. 48 (2009) 296.
[127] C.B. Gao, H.Q. Zheng, L. Xing, M.H. Shu, S.N. Che, Chem. Mater. 22 (2010) 5437.
[128] ISP Pharmaceutical Technical Bulletin, CAVAMAX® Native Cyclodextrins, http://online1.ispcorp.com/Brochures/Pharma/CAVAMAX%20Native%20Cyclodextrins%20Product%20Overview.pdf.
[129] U. Gupta, N.K. Jain, Adv. Drug Deliv. Rev. 62 (2010) 478.
[130] V. Lassalle, M.L. Ferreira, Macromol. Biosci. 7 (2007) 767.
[131] Y. Lu, S.C. Chen, Adv. Drug Deliv. Rev. 56 (2004) 1621.
[132] M. Kumar, J. Pharm. Pharm. Sci. 3 (2000) 234.
[133] U. Gupta, H.B. Agashe, A. Asthana, N.K. Jain, Biomacromolecules 7 (2006) 649.
[134] P. Couvreur, C. Vauthier, Pharm. Res. 23 (2006) 1417.
[135] P.R. Lockman, R.J. Mumper, M.A. Khan, D.D. Allen, Drug Dev. Ind. Pharm. 28 (2002) 1.
[136] W.J. Rieter, K.M. Pott, K.M.L. Taylor, W.B. Lin, J. Am. Chem. Soc. 130 (2008) 11584.
[137] K.M.L. Taylor-Pashow, J. Della Rocca, Z.G. Xie, S. Tran, W.B. Lin, J. Am. Chem. Soc. 131 (2009) 14261.
[138] P. Horcajada, T. Chalati, C. Serre, B. Gillet, C. Sebrie, T. Baati, J.F. Eubank, D. Heurtaux, P. Clayette, C. Kreuz, J.S. Chang, Y.K. Hwang, V. Marsaud, P.N. Bories, L. Cynober, S. Gil, G. Férey, P. Couvreur, R. Gref, Nat. Mater. 9 (2010) 172.
[139] A.R. Thierry, D. Vige, S.S. Coughlin, J.A. Belli, A. Dritschilo, A. Rahman, Faseb J. 7 (1993) 572.
[140] A. Layre, R. Gref, J. Richard, D. Requier, P. Couvreur, FR 04 07569, 2004.
[141] J.T. Slattery, J.E. Sanders, C.D. Buckner, R.L. Schaffer, K.W. Lambert, F.P. Langer, C. Anasetti, W.I. Bensinger, L.D. Fisher, F.R. Appelbaum, J.A. Hansen, Bone Marrow Transpl. 16 (1995) 31.
[142] Z. Hassan, C. Nilsson, M. Hassan, Bone Marrow Transpl. 22 (1998) 913.
[143] I. Imaz, J. Hernando, D. Ruiz-Molina, D. Maspoch, Angew. Chem. Int. Ed. Engl. 48 (2009) 2325.

[144] I. Imaz, M. Rubio-Martinez, L. Garcia-Fernandez, F. Garcia, D. Ruiz-Molina, J. Hernando, V. Puntes, D. Maspoch, Chem. Commun. 46 (2010) 4737.
[145] R.C. Rowe, P.J. Sheskey, S.C. Owen, Handbook of Pharmaceutical Excipients, fifth ed., Pharmaceutical Press, Great Britain and American Pharmacists Association, Washington, 2006.
[146] M. Gibson, Pharmaceutical Preformulation and Formulation – A Practical Guide from Candidate Drug Selection to Commercial Dosage Form, Interpharm/CRC, Boca Raton, 2004.
[147] A.C. McKinlay, R.E. Morris, P. Horcajada, G. Férey, R. Gref, P. Couvreur, C. Serre, Angew. Chem. Int. Ed. Engl. 49 (2010) 6260.