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

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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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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.

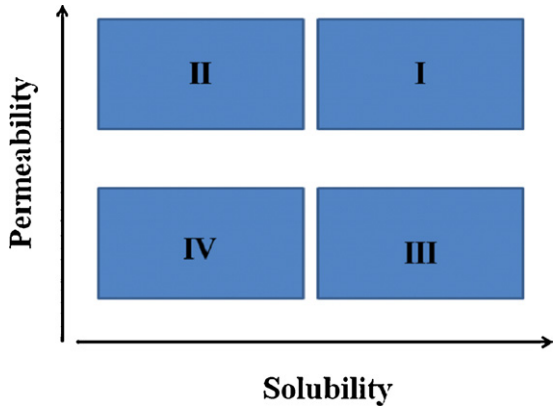

Fig. 1. Biopharmaceutical Classification System (BCS) of drugs based on solubility and permeability.

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