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Rise of a New Drug Delivery System: Covalent Organic Framework

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Abstract

Covalent organic framework (COF) is a kind of two- or three-dimensional crystalline porous materials connected by strong covalent bonds. With uniform pore size distribution, controllable pore size, high porosity, functionalized surface chemical as well as physical and chemical stability, COF is emerging as a drug delivery system. In this commentary, the rise of COF as a drug-delivery carrier was briefly reviewed.

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Introduction

Based on solvothermal synthesis, ionothermal synthesis, microwave synthesis, mechanochemical synthesis and room-temperature synthesis, covalent organic framework (COF) is a kind of two- or three-dimensional crystalline porous materials connected by strong covalent bonds (B-O, C-C, C-H and C-N) [1-3]. COF is often composed of light elements, with low skeleton density, large surface area, high porosity, uniform pore size distribution, controllable pore size, functionalized surface chemical as well as physical and chemical stability [2]. Compared with metal organic framework (MOF), the covalent bonds improve the chemical and thermal stability of COF, and the composition of non-metallic element makes the density of the COF lower. Compared with the amorphous porous material, the ordered crystalline porous structure has the characteristics of designability, clipping and functionalization. Meanwhile, COF avoids the toxicity caused by metal elements, thus it owns the incomparable biocompatibility and biodegradability to those of other materials [4].

Advantages Endow COF

These advantages endow COF strong application potentials in heterogeneous catalysis [5], gas adsorption and storage [6], selective separation [7], semiconduction and photoconductor [8-10]. And in recent years, COF has been widely explored as a drug delivery carrier [11-13]. An ideal drug delivery carrier for in vivo application requires optimal particle size and drug loading, controlled drug release as well as good biocompatibility. The unique physical and chemical properties of COF provide a new possibility for the development of drug delivery systems.

The first COF used for drug carrier was two kinds of 3D polyimide COF (PI-COF-4 and PI-COF-5) with different pore sizes, with the drug loading more than 20%. In vitro release showed that both COF effectively controlled the dissolution of ibuprofen and realize the sustained release [12]. Porphyrin-based covalent organic frameworks (PCTFs) was also used as a drug delivery system. With the interaction between the acidic group modified in IBU and the triazine ring of COF, the controllable encapsulation and release of the drug were realized, and the amount of drug loaded was over 17% while more than 90% of drug released within 48 h. Meanwhile, the result of cytotoxicity of PCTFs showed that Porphyrin-based COF had high biocompatibility and could be used as an ideal carrier [14]. Compared to previously reported COF, the schiff-base COF has been widely explored for the drug carriers. Zhao and co-workers prepared imine-linked 2D COF (PI-2-COF and PI-3-COF). Both kinds of COF showed high drug loading capacity and even reaching to 30 wt%. More importantly, these COF were uniform spherical nanoparticles with a diameter of 50 nm. These features made carriers in a suitable size for cellular uptake and in vivo drug delivery. Confocal images showed the effective uptake of drug-loaded COF by the cells. After incubation with the 5-Fu-loaded COF for 48 h, the cell survival rate was less than 10%.

Based on these achievements, Zhang and co-workers [15] developed a water-dispersible polymer-COF nanocomposites through the assembly of polyethylene-glycol-modified monofunctional curcumin derivatives and aminefunctionalized COF (PEG-CCM@APTES-COF-1). In vitro and in vivo studies demonstrated that PEG-CCM@APTES-COF-1 is a smart carrier for drug delivery with superior stability, intrinsic biodegradability, high DOX loading capacity, strong and stable fluorescence, prolonged circulation time and improved drug accumulation in tumors. However, most of the studies of drug delivery systems based on COFs are based on the mechanism of enhanced permeability and retention (EPR) effect to deliver drugs in vivo [15]. Only about 5% of nanoparticles can reach the tumor target in the study of PI-3-COF carrier, and the tissue targeting ability of the drug delivery system was low [11,16]. Modification with targeting ligands is a possible way for the application expansion and performance improvement of COF in vivo. Banerjee and co-workers prepared the targeted drug delivery of COF (TpASH-FA) through the modification of covalent organic nanosheets with folic acid. Although the drug loading capacity of TpASH-FA was 12% lower than that of many other COF, it exhibited pretty targeted drug delivery. The survival rate of cells was significantly reduced under low dose administration [13].

As drug-delivery carriers, COF has made encouraging progresses, but the challenges still remain. From the point of the preparation of COF, the growth process, crystallization mechanism and reaction kinetics, as well as the control of the growth and morphology on

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the micro scale of COF is unclear now. Moreover, the complexity of preparation methods and the long preparation cycle limit the development of COF. In the terms of drug-delivery carriers, the formability and dispersibility of COF need to be improved. The pore size and morphology of COF must meet the requirements of drug carriers. More seriously, although several studies have tested the efficacy of COF formulations and their safety, there are little is known about the fate of COF in vivo when it finished the delivery of the cargo to the targeted site, and their long-term accumulation and degradation profiles were not carried out. In addition, it is necessary to establish a complete in vivo and in vitro evaluation system for the development of COF formulations.

Summary

In summary, the inherent advantages of COF provide new ideas for the development of drug delivery systems. And we believe that with the creativity and inventiveness of scientists continuous improvements in the design and detailed investigations on their in vitro and in vivo behaviors of COF will help it develop as nanocarriers from bench to bedside.

Competing Interests

The authors declare that they have no competing interests.

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