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Review

Cyclodextrin-Mediated Hierarchical Self-Assembly and Its Potential in Drug Delivery Applications

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ABSTRACT

Hierarchical self-assembly exploits various non-covalent interactions to manufacture sophisticated organized systems at multiple length scales with interesting properties for pharmaceutical industry such as possibility of spatially controlled drug loading and multiresponsiveness to external stimuli. Cyclodextrin (CD)-mediated host-guest interactions proved to be an efficient tool to construct hierarchical architectures primarily due to the high specificity and reversibility of the inclusion complexation of CDs with a number of hydrophobic guest molecules, their excellent bioavailability, and easiness of chemical modification. In this review, we will outline the recent progress in the development of CD-based hierarchical architectures such as nanoscale drug and gene delivery carriers and physically cross-linked supramolecular hydrogels designed for a sustained release of actives.

Introduction

Hierarchical self-assembly is traditionally defined as non-covalent organization of molecules and macromolecules which takes places over distinct, usually increasing, length scales, whereby the non-covalent interactions at each subsequent length scale gradually decrease in strength.[1] The range of length scales spans from sub-nanometer to micrometer and even macroscopic and the involved interactions include, but are not limited to, electrostatic assembly, hydrogen bonding, van der Waals forces, and host-guest complexation. A classic example of hierarchical self-assembly from nature is the formation of collagen fibers, where 3 polypeptide chains initially self-assemble into a nanometric triple helix and further, through a synergetic combination of hydrogen bonds, van der Waals interactions, and sparse disulfide bonds between cysteine residues, end up as cord-shaped collagen fibers of 1-20 microns in diameter (Fig. 1).[2,3]

In the last 20-30 years, a fast development of the supramolecular chemistry has occurred; the latter exploits weak non-covalent interactions to prepare sophisticated intermolecular ensembles.[4] Thereby, along with establishing deeper understanding of the processes taking place in nature, researchers obtained a tool to produce smart hierarchically organized systems artificially. Due to a number of advantages such as high flexibility, multifunctionality, and structural responsivity to various external stimuli, artificial hierarchically organized systems might find applications as high performance catalysts,[5] integrated parts of chemical sensors,[6] or drug delivery vehicles.

The construction elements used in hierarchical self-assembly are not limited to biopolymers and soft matter materials. To date, a considerable number of purely inorganic hierarchically structured materials have been described.[7] Those include zeolite catalysts with dual micro/mesoporosity, environmental photocatalysts,[8,9] and active elements in photovoltaics.[10] The benefits of hierarchical organization in such systems compared to their conventional analogs are due to the enhancement of mass transport of substrate molecules or photopollutants in the cases of zeolites or photocatalysts respectively.[11-13]

Also, a vast body of work has been dedicated to the development of hierarchical inorganic-organic hybrids. The most prominent examples include metal-organic frameworks (MOFs) with double porosity,[5] graphene-based hybrids for energy storage devices,[11] and self-healing hybrid hydrogels reinforced with inorganic

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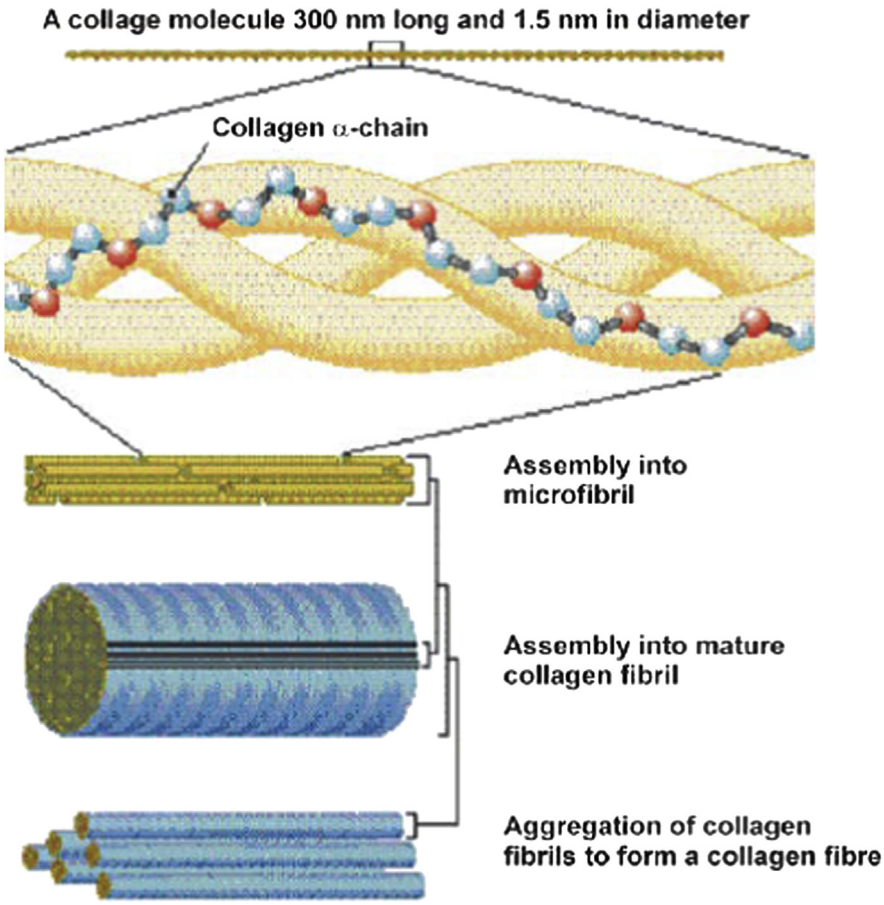

Figure 1. Levels of hierarchical self-assembly of collagen. Reproduced from Elemans et al.[3]

nanoparticles.[12] As in the case with microporous zeolites, hierarchical structuring of MOFs at meso/macroscopic length scales leads to a synergetic increase in their performances as drug delivery vehicles,[13,14] catalysts,[5] or integrated parts of chemical sensors.[6]

Albeit, due to their versatility and functionality, soft matter building blocks are prevalent in artificially prepared nanoarchitectures. Despite the immense variety and complexity of soft hierarchical systems, some basic classification appears to be possible.

Peptides and peptide-based polymeric materials are admittedly the most popular building blocks in hierarchical self-assembly. Chemical information encoded in peptide chains allows them to efficiently self-organize across multiple length scales in a controlled fashion.[15] Specifically tailored peptide-based hierarchical systems found applications as scaffolds in regenerative medicine,[16] templating vessels for biomineralization,[17] and drug or gene delivery vehicles.[18,19]

Another class of valuable building blocks for construction of hierarchical architectures is nucleic acids. Self-assembly properties of nucleic acids such as DNA and RNA are based on weak but specific hydrogen bonding between 4 distinct naturally occurring nucleotides.[20,21] Artificial modifications of nucleotide sequences allow hybridization of nucleic acids into secondary structures unknown in nature, for example, two-dimensional tiles and lattices.[20] Another powerful strategy consists in preparation of DNA block copolymers (DBCs), where DNA strands are covalently linked to various hydrophobic polymer blocks.[21,22] Like conventional amphiphilic block copolymers, DBCs form various nanometric architectures in water, such as micelles,[22] cylinders,[23] or polymersomes.[24] The DNA corona on top of DBC-based nanostructures allows for their functionalization and extension with complementary nucleic acid strands attached to nanoparticles, drugs, or dyes.[23]

The third group of soft hierarchically structured materials is based on ionic self-assembly (ISA) of polyelectrolytes (PE) with surfactants, amphiphilic block copolymers containing PE charge-carrying blocks,[25] or polymeric ionic liquids.[26] A wide range of materials prepared by hierarchical ISA include liquid-crystalline, porous, hybrid organic-inorganic,[27] and electroactive materials.[25] Moreover, ISA is used in gene delivery as a mean of DNA compaction by positively charged gene vectors.[28]

Host-guest or inclusion interactions arise as a result of synergy between non-polar van der Waals forces, hydrogen bonding, and precise matching in size between a guest molecule and the hydrophobic cavity of a macrocyclic host. The sterical and chemical requirements to guest molecules constitute the basis of the so-called “molecular recognition” phenomenon. The latter leads to high specificity and controllability of host-guest interactions, as opposed to simple electrostatic, hydrophobic, or hydrogen binding.[29-31] Additionally, host-guest complexes formation and dissociation are sensitive to environmental changes such as temperature, light, mechanical pressure, or competitive guests binding.[29] Due to these features, inclusion complexation has been employed for construction of a significant number of smart hierarchically structured architectures.[31-33]