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REVIEW

Building nanostructures with drugs

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Abstract The convergence of nanoscience and drug delivery has prompted the formation of the field of nanomedicine, one that exploits the novel physicochemical and biological properties of nanostructures for improved medical treatments and reduced side effects. Until recently, this nanostructure-mediated strategy considered the drug to be solely a biologically active compound to be delivered, and its potential as a molecular building unit remained largely unexplored. A growing trend within nanomedicine has been the use of drug molecules to build well-defined nanostructures of various sizes and shapes. This strategy allows for the creation of self-delivering supramolecular nanomedicines containing a high and fixed drug content. Through rational design of the number and type of the drug incorporated, the resulting nanostructures can be tailored to assume various morphologies (*e.g.* nanospheres, rods, nanofibers, or nanotubes) for a particular mode of administration such as systemic, topical, or local delivery. This review covers the recent advances in this rapidly developing field, with the aim of providing an in-depth evaluation of the exciting opportunities that this new field could create to improve the current clinical practice of nanomedicine.

Introduction

The construction of complex supramolecular architectures through the self-assembly of basic molecular building blocks is a strategy that can be both practical and inspiring,

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affording nanostructures with properties that the individual unit does not necessarily possess [1]. Nature leads the way in harnessing the power of molecular assembly, as exemplified by the folding of polypeptide chains into functional proteins capable of specifically recognizing important biomolecules and mediating many biological events [2,3], forming the dynamic cytoskeletons from tubulins and actins essential for cellular and subcellular functions [4,5], and creating hair, nails, hooves and horns from the multilevel assembly of keratin proteins [6,7]. Inspired by these exquisite assembly systems, the accumulated knowledge from over fifty years of research has enabled the creation of a wide range of supramolecular structures from an ever expanding set of natural and synthetic building blocks, including small synthetic molecules [1], block copolymers [8–11], rationally designed peptides [12–18], carbohydrates [19], proteins [20] and DNA [21,22]. Concurrently, functional utilization of these supramolecular nanostructures has been extensively explored in diverse areas, particularly in the context of drug delivery [23–25]. The control over the size, morphology, surface chemistry, internal structures, and stability (including both disassembly kinetics and pathways) of supramolecular nanostructures bestows the potential to carry, protect and release a therapeutic cargo in a highly regulated manner [26–28]. This carrier–cargo relationship is based on a separation of function, however, with the molecular building blocks purely responsible for delivery (assuming biocompatibility and inertness) and the drug for the ensuing bioactivity. Once its function has been fulfilled the carrier is considered waste material that needs to be cleared.

An emerging approach for the delivery of therapeutic agents has been to consider the drug itself as a key component of the self-assembly possessing the potential to create its own nanostructures. In this way, extraneous materials can be avoided without loss of function, perhaps leading to more effective therapies due to the increased drug loading, elimination of the leakage issue associated with encapsulated drugs, and the reduced need to remove synthetic carrier material. What is unclear is the extent to which the potential intermolecular interactions afforded by a drug's molecular structure can be harnessed to allow the rational design of a particular nanostructure and how general this approach can truly be given the wide range of structural types in clinical use. This review will discuss a number of strategies that have been adopted in which small molecule drugs have been utilized as building blocks in the construction of their own nanostructures, with an emphasis on those that involve *true self-assembly pathways*. In this context, molecular assembly is interpreted as the spontaneous and reversible association of molecules into aggregates (*e.g.* molecular clusters, discrete morphologies, or three dimensional networks) in order to minimize system free energy. It is important to note that nanostructures created through molecular self-assembly are distinct from those prepared by precipitation or emulsion methods in that the physiochemical properties of the former (*e.g.* size, shape, internal order, stability, aggregation number, surface chemistry) are reflective of the molecular characteristics of the building units and the assembly conditions. It is the interplay of the systemic entropy with the enthalpic interactions among the building units, water, and other molecules present in the assembly system that defines the eventual self-assembled morphology. We believe that the rapidly growing area of drug-promoted molecular assembly holds great promise for future research in nanomedicine and cancer chemotherapy, harnessing the intrinsic molecular interactions of a drug to build its own nanocarrier that, to paraphrase Lehn's definition of supramolecular chemistry [29], provides ''functions beyond the drug''.

Nanostructure formed by free drugs

Small molecule drugs exhibit a wide range of chemical structures that determine how their solubility, aggregation, and transportation behavior in solution ultimately determine their pharmacokinetic profiles after administration and pharmacodynamics in interfacing with their biological targets. Large hydrophobic moieties, such as hydrocarbons or polyaromatic segments that possess strong self-associative interactions, can lead to solubility problems and a high propensity for self-aggregation in aqueous solution, whereas a number of charged groups, *e.g.* carboxylates or amines, bestow a greater solubility and reduce the potential for self-association. The study of the self-association behavior of drug molecules and potential candidates is an important subject in pharmaceutical research [30]. Knowledge of how these molecules interact with themselves will aid in improving their efficacy, in understanding their pharmacokinetic profile, and in developing the most suitable formulation for administration. For example, Shoichet and coworkers investigated the aggregation behavior of seven hydrophobic anticancer drugs and found that the formation of colloidal particles inhibited the *in vitro* cytotoxic potential [31]. These colloidal structures could be disrupted in the presence of surfactants, restoring the respective drug's toxicity. It was also found that the colloidal forms exhibited greater interactions with proteins, such as albumin, causing unpredictable pharmacokinetic behavior.

Drugs that are amphiphilic, containing well separated large hydrophobic and charged groups, could demonstrate reversible self-assembly behavior, resulting in formation of dynamic molecular clusters or even discrete supramolecular nanostructures of well-defined size and shape. For example, anthracyclines, a class of antibiotic-based antineoplastics characterized by a hydrophobic planar anthraquinone moiety and a hydrophilic amino-sugar ring (Fig. 1), possess decent aqueous solubility due to the ionizable amine group and are commonly observed to exist as dimers and higher oligomers in solution [32–35]. Studies suggest that these dimers exist in parallel and antiparallel orientations of the molecules [33,34]. It has been postulated that the structural differences in the packing among the various derivatives, *e.g.* daunomycin, Adriamycin (Doxorubicin), 4′-epiadriamycin, may account for the variation in pharmacological activity [34]. Hayakawa and coworkers have also reported the formation of doxorubicin-based hydrogels through the use of high NaCl concentrations [36], which induce further self-association *via* $\pi-\pi$ stacking of the aggregates. Similar dimerization behavior was also found for the anthracycline-alternative mitoxantrone [37], and for the water-soluble camptothecin derivative irinotecan (CPT-11) [38].

Folic acid, also known as vitamin M or B_9, is another example that illustrates a drugs' self-assembling potential.