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Bioinspired drug delivery systems

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The way Nature designs, processes and assembles molecular building blocks to fabricate high performance materials with a minimum of resources is a suitable model for the design of drug delivery systems (DDS) with advanced functionalities. Bioinspired preparation methods that involve the use of superhydrophobic surfaces, layer-by-layer assembly or protein-driven growth are being successfully implemented to create a wide range of polymeric and hybrid structures. Mimicking the surface, shape, texture and movement of cells and microorganisms help to overcome phagocytosis and attain efficient targeting of the drug carriers, while transposition of the feed-back regulation mechanisms and the functions of membrane channels and physiological receptors may notably enhance the spatiotemporal control of drug release. These aspects are addressed in the present review.

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Introduction

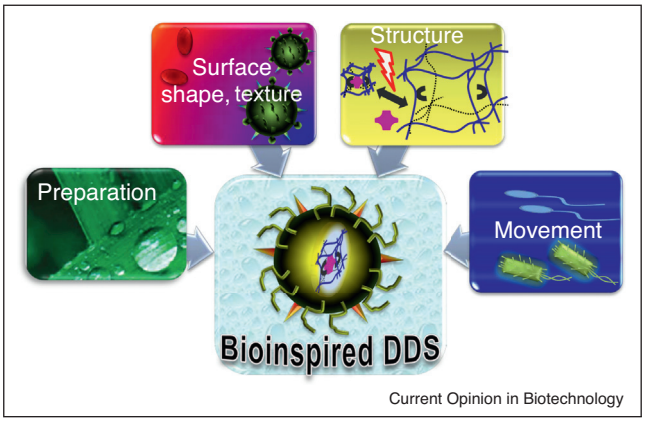
Pharmaceutical technology has experienced a remarkable evolution in the last decades searching for overcoming the solubility/stability limitations associated to the novel active substances of biotechnological origin, and improving the efficiency/safety profiles of old and new drugs by means of targeting to the required tissue or cell structure [1]. Advanced dosage forms are now conceived to behave not only as the 'hardware' that facilitates the handling and the administration of the drug and regulates the local or systemic release, but also as the 'software' that should sense the microenvironment through which the drug has to pass in the route towards the action site, in order to help the drug to overcome certain barriers, and fit the release process to specific therapeutic demands. Namely, they can be seen as true carriers able to deliver the drug at the best conditions as possible to the absorption site, and to modulate drug distribution in the body and its clearance [2]. An advanced drug delivery system (DDS) should behave as a 'self-delivery' packet (the pilot plus the cargo) that enables the targeted delivery and the achievement of therapeutic levels in specific organs, tissues or even cellular structures, when they are required [3,4••].

Transport and recognition processes inside the body serve as excellent models for the design of DDS. Evolution has led to the most efficient systems by just combining few amino acids, saccharides and lipids. Biological molecules perform incredibly complex functions, adopting architectures which are the result of the correct assembly of components that interact with high specificity in extremely small length scales [5]. Nowadays chemistry offers millions of monomers to be used as components of synthetic molecules. Finding the appropriate sequence is the key for generating biomimetic systems. Biomimetics has been recently defined as an emerging field of science that includes the study of how Nature designs, processes and assembles/disassembles molecular building blocks to fabricate high performance soft materials and mineral-polymer composites, and then applies these designs and processes to engineer new molecules and materials with unique properties [6]. Mimicking molecule-selective agents, camouflage coatings/shells or stimuli-sensitive components are already greatly impacting the design of tailored DDS by deriving benefit from interdisciplinary knowledge [7•,8••]. Application of the biomimetic principles can not only render drug carriers with bioinspired structure and/or functionality, but also novel ways to prepare the carriers (Figure 1).

Bioinspired procedures to prepare DDS

Conventional encapsulation methods (e.g. evaporation/extraction, coacervation, interphase polymerization) usually involve two or more phases and quite harsh conditions to trigger the encapsulation, which may compromise the stability of labile drugs and certainly prevent the obtaining of a high encapsulation yield because of migration/diffusion to external liquid phases. Detailed analysis of the superhydrophobic surfaces of certain plant leaves and insect wings [9] has enabled the implementation of surface treatment processes that reproduce their characteristic hierarchical structure on synthetic materials [10••]. As the water drops roll on the Lotus leaves, dispersions of monomers/polymers containing the drug can be applied (with a pipette or a nozzle) on superhydrophobic surfaces of copper, aluminum or polystyrene to render, after polymerization/cross-linking, nearly perfect spherical particles (Figure 2a). Since the process takes place at the solid–air interface, no migration of

Figure 1



Mimicking natural processes, structures and functions provides drug delivery technology with tools useful to design and prepare more efficient targeted, stimuli-responsive drug carriers.

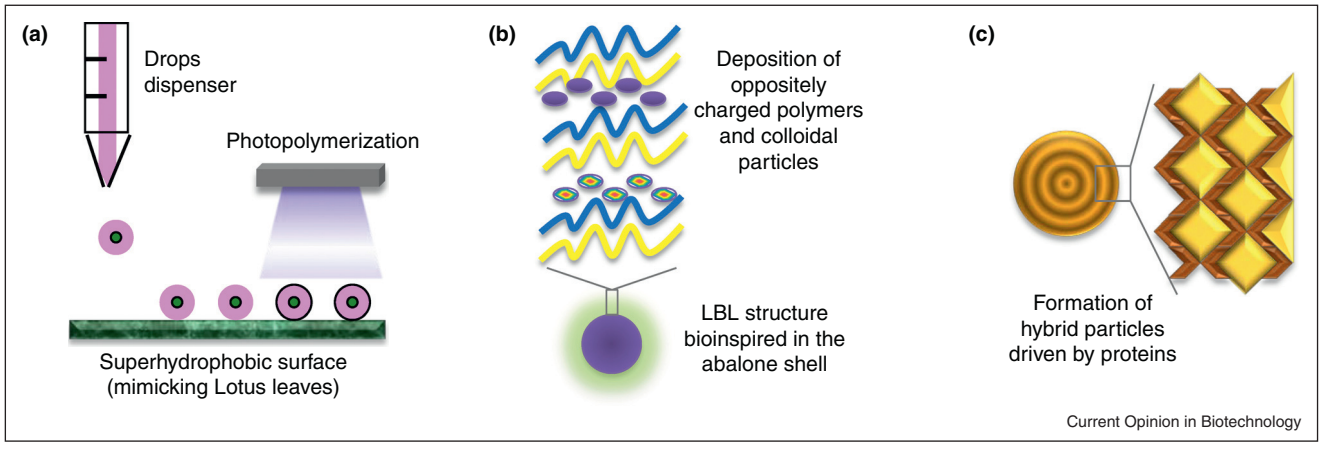
the drug occurs, and thus 100% encapsulation yield is feasible. The versatility of this approach has been already demonstrated by preparing semi-interpenetrating poly(N-isopropyl acrylamide)/dextran microgels that encapsulate proteins and can control the release for several hours [11]. Deposit of additional drops onto preformed micro/nano-gels leads to multilayered systems for simultaneous modulation of the release of various therapeutic substances [12].

On the other hand, the layer-by-layer (LBL) approach typically mimics the bottom-up way the Nature uses to build a variety of structures (Figure 2b). Through versatile combinations of interaction forces (i.e. electrostatic, hydrophobic, hydrogen bonding or biological recognition) and of materials (e.g. polymers, peptides and nanoparticles) it is possible to finely control the nanometer-scale order, location and concentration of the components in drug carriers [13]. The release of the therapeutic substances trapped in the layers depends on the permeability or the breakdown of the multilayer structure, and can be programmed to occur when a stimulus disintegrates or triggers the dissolution of the assembly. *In vivo* tests have proved the enormous potential of LBL in the fields of drug, gene, and vaccine delivery and cancer imaging, notably enhancing the bioavailability of chemotherapeutic compounds and short interfering RNA (siRNA) [14]. Mimicking of the natural morphogenesis of hard tissues such as the shells of mollusks or human teeth or bones, can render improved hybrid materials (Figure 2c). The proteins that drive the depositions of phosphates or silica in the natural processes (i.e. genetically engineering proteins for inorganics, GEPI) may also help to regulate the composition, geometry and macro-pore/micro-pore structure of inorganic-based composites suitable for drug-delivery prosthetic materials and systemic nanovehicles [15].

Bioinspired surfaces for target nanocarriers

Nanotechnology is greatly impacting therapeutics enabling the development of DDS that can reach otherwise inaccessible cell structures [16]. However, the clinical success of the nanocarriers is limited by adverse events that occur at the biological environments: blood stream (e.g. opsonization and precipitation by proteins may prevent the nanocarrier from reaching the endothelium), tissue matrix (rich in lipids and, if pathological, also in proteolytically cleaved peptides, oligosaccharides, cytokines, and growth factors that may compromise the stability of the carrier), and target cells with efflux pumps to expel untoward substances (Figure 3). To overcome

Figure 2



Some bioinspired approaches to prepare DDS: drop deposition of drug-containing polymer solutions on superhydrophobic surfaces followed by polymer hardening **(a)**, successive deposition of layers of oppositely charged polymers and colloidal structures **(b)**, and deposition of inorganic materials driven by proteins **(c)**.