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Research review paper

Drug nano-reservoirs synthesized using layer-by-layer technologies

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ABSTRACT

The pharmaceutical industry has been able to tackle the emergence of new microorganisms and diseases by synthesizing new specialized drugs to counter them. Their administration must ensure that a drug is effectively encapsulated and protected until it reaches its target, and that it is released in a controlled way. Herein, the potential of layer-by-layer (LbL) structures to act as drug reservoirs is presented with an emphasis to "nano"-devices of various geometries, from planar coatings to fibers and capsules. The inherent versatile nature of this technique allows producing carriers resorting to distinct classes of materials, variable geometry and customized release profiles that fit within adequate criteria required for disease treatment or for novel applications in the tissue engineering field. The production methods of LbL reservoirs are varied and allow for different kinds of molecules to be incorporated, such as antibiotics, growth factors and biosensing substances, not limited to water-soluble molecules but including hydrophobic drugs. We will also debate the future of LbL in the pharmaceutical industry. Currently, multilayered structures are yet to be covered by the regulatory guidelines that govern the fabrication of nanotechnology products. However, as they stand now, LbL nanodevices have already shown usefulness for antifouling applications, gene therapy, nanovaccines and the formation of de novo tissues.

Contents

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1. Introduction

The emergence of new diseases and microorganism strains demands constant evolution and research in the field of drug delivery and nanomedicine. The most straightforward strategy adopted by the pharmaceutical industry has been the synthesis of new drugs that may hopefully fight against these pathologies. In turn, this triggers the demand for appropriate drug carriers that can effectively be loaded with and protect the drugs until they are administered and delivered. There is a multitude of carriers that have been used, including micelles, liposomes, polymersomes or polymer particles/capsules (Blanazs et al., 2009; Costa and Mano, 2014; Lima et al., 2012; Malam et al., 2009; Meng et al., 2009; Szarpak et al., 2010) but there are still drugs which these strategies fail to encapsulate efficiently (e.g., hydrophobic and short biofunctional peptides). Thus, drug delivery faces a few challenges: (i) to elaborate advanced new functional drugs and nanodrugs, (ii) to develop delivery systems capable of encapsulating water-insoluble drugs, and (iii) to develop drug delivery systems that provide a sustained release of a drug within a desired therapeutic window in order to ensure its efficacy (Antipov et al., 2001; Vergaro et al., 2011). Some diseases, like cancer, demand extra needs, since the administration of chemotherapeutics faces problems like non-specificity, toxic effects and lack of localized administration strategies (Jain and Stylianopoulos, 2010).

The synthesis and design of drug delivery devices have experienced great advances towards new sustained and controlled delivery systems for a safe and efficient administration. These include long-term stability, high loading capacity and site selectivity. Other desired properties include the capability of a carrier to control the delivery of multiple biological compounds at independent time scales and to release them within a therapeutic window (Chung and Rubner, 2002; Pavlukhina and Sukhishvili, 2011; Radt et al., 2004).

Recently, scientists and engineers worldwide have begun to adopt biomimetic concepts that take natural structures as inspiration to develop new drug delivery devices, by mimicking not only their function but also their architecture. One inspirational example is the layered organization of nacre found in sea animal shells, which provide mechanical strength (Luz and Mano, 2009). One can envisage the development of layered structures in a laboratorial environment that exhibit other functionalities, depending on their ultimate application. Scientists have developed a strategy by which polyelectrolytes are alternately adsorbed onto solid surfaces (Decher and Hong, 1991; Decher et al., 1992; Iler, 1966). This technique is known as layer-by-layer (LbL), and in the last two decades it has provided a reliable, easy, versatile and cost-effective way of modifying surfaces for tuned cell adhesion, drug delivery and improved implant biointegration. LbL relies on the use of materials – belonging to virtually any material class, from inorganic compounds (e.g., nanoparticles and carbon nanotubes) (Mamedov et al., 2002; Srivastava and Kotov, 2008; Upadhyayula and Gadhamshetty, 2010) to polymers (including synthetic and natural-based macromolecules) (Boddohi et al., 2008; He et al., 2008) – sequentially assembled by spontaneous adsorption and forming robust coatings.

Films fabricated via LbL can be assembled on top of not only 2D planar substrates but also on convoluted and 3D geometries. In all cases, the sole requirement for this reaction to occur spontaneously is the exhibition of complementary interactions between the various selected building blocks — such as electrostatic contacts, van der Waals forces, and hydrogen bonds (Borges and Mano, 2014; Boudou et al., 2010; Costa and Mano, 2014; Decher, 1997; Hammond, 2011; McClements, 2006; Tang et al., 2006). Table 1 summarizes the different devices that result from LbL being applied to different geometries (see also Section 3). The assembled films may then provide in both cases a matrix capable of acting as drug reservoirs. Thanks to this versatility of LbL, it is possible to construct planar films, three-dimensional multilayered capsules (PMCs) and nanotubes by assembling the constituents around leachable sacrificial templates (Fig. 1). Additional characteristics include the lack of necessity to resort to organic solvents and biological aggressive processing conditions (e.g., high temperatures, extreme pH values), making LbL an attractive strategy to be coupled with biological applications. Specialized biomaterials and ligands, such as cell adhesion enhancers, may be added in order to render a substrate more instructive for cell adhesion, proliferation and differentiation (Costa et al., 2011; Gribova et al., 2013; Oliveira et al., 2013). Furthermore, significant efforts have been made to design coatings and PMCs capable of loading and releasing small molecules, drugs and biomolecules, in conjugation with both current and cutting-edge biomedical devices, such as implants and catheters (Karlsson et al., 2010; Lichter et al., 2009; Wang et al., 2009b).

In this critical review, the LbL strategy will be presented as a technique able to conceive various multilayered systems with potential use in drug delivery. We will focus in biomedical applications that require a high level of control of drug administration, such as in biosensing, microenvironments confining chemical reactions, and microtissue production (De Koker et al., 2011; Gribova et al., 2012; McShane and Ritter, 2010; Tong et al., 2012). PMCs with a few micrometers in diameter are often based on microtemplates that are convenient and easy to use, thus being considered the gold-standard of LbL strategies for drug delivery. The topic of micrometric PMCs has been often nicely reviewed (Becker et al., 2010; De Koker et al., 2011; Shchukina and Shchukin, 2011; Tong et al., 2012; Vergaro et al., 2011; Wohl and Engbersen, 2012). Herein, we will focus on drug reservoirs consisting of planar coatings (Section 3.1), nanometric PMCs, which among other properties offer a higher surface area per unit weight than larger PMCs (Section 3.2), and nanotubes (Section 3.3). It is also our intention to show the readers how such an approach is capable of rivaling with some of the most common drug administration systems currently in use, focusing on reports about potential applications published mostly in the last 5 years (Section 5). Despite the tremendous efforts, only in recent years have LbL constructs reached a level where the fabrication parameters and drug encapsulation strategies are well-known. It is now possible to fabricate LbL devices with properties that are desirable for an efficient systemic delivery and that can be reproduced with great reliability, which include low toxicity, stability in various aqueous environments, prolonged release of drugs in vitro and in vivo and targeted delivery (Shutava et al., 2014). Due to the potential benefits that LbL devices can bring to the healthcare sector, the current regulatory status of LbL devices and nanomaterials will be discussed in Section 6.

2. Layer-by-layer as a drug reservoir construction tool

LbL is often regarded as a surface engineering technique, grouped together with other surface engineering approaches, such as plasma surface modification (Chu et al., 2002), polymer grafting (Kato et al., 2003), micro/nanofabrication (Lu and Chen, 2004) and Langmuir–Blodgett (Zasadzinski et al., 1994). All these surface engineering tools aim to modify the properties of interfaces while retaining the properties of the bulk materials. Although primarily appreciated as a surface engineering technique, the use of LbL to encapsulate bioactive substances makes it identifiable as a method to fabricate drug delivery reservoirs, capable of solving many problems of conventional devices, such as hydrogels (premature disintegration of the matrix) (Hoare and