Journal of Controlled Release xxx (2014) xxx–xxx

Contents lists available at ScienceDirect

Journal of Controlled Release

journal homepage: www.elsevier.com/locate/jconrel

Review

Engineering and evaluating drug delivery particles in microfluidic devices

Mattias Björnmalm, Yan Yan, Frank Caruso *

Department of Chemical and Biomolecular Engineering, The University of Melbourne, Melbourne, Victoria 3010, Australia

ARTICLE INFO

Article history:
Received 6 February 2014
Accepted 21 March 2014
Available online xxxx

Keywords:
Nanomedicine
Nanoparticles
Microfluidics
In vitro/*in vivo* model

ABSTRACT

The development of new and improved particle-based drug delivery is underpinned by an enhanced ability to engineer particles with high fidelity and integrity, as well as increased knowledge of their biological performance. Microfluidics can facilitate these processes through the engineering of spatiotemporally highly controlled environments using designed microstructures in combination with physical phenomena present at the microscale. In this review, we discuss microfluidics in the context of addressing key challenges in particle-based drug delivery. We provide an overview of how microfluidic devices can: (i) be employed to engineer particles, by providing highly controlled interfaces, and (ii) be used to establish dynamic *in vitro* models that mimic *in vivo* environments for studying the biological behavior of engineered particles. Finally, we discuss how the flexible and modular nature of microfluidic devices provides opportunities to create increasingly realistic models of the *in vivo* milieu (including multi-cell, multi-tissue and even multi-organ devices), and how ongoing development toward commercialization of microfluidic tools are opening up new opportunities for the engineering and evaluation of drug delivery particles.

Contents

1. Introduction

Through nanotechnology, synthetic functional structures can be engineered at the nanometer-level, thus creating materials that can interact with, and influence, biological systems at their very core [1]. The application of nanotechnology to diagnose and treat diseases – nanomedicine – has moved from being solely an academic endeavor to making an impact in the clinic [2]. Examples include: (i) biomaterials for medical implants, such as nanocomposites used as dental fillers; (ii) *in vitro* diagnostics, such as gold nanoparticles that enhance sensitivity in genetic assays; (iii) *in vivo* imaging, such as superparamagnetic iron oxide nanoparticles for use as contrast agents in magnetic resonance imaging; and (iv) drug delivery, where nanostructured carriers can be used for the controlled delivery of therapeutics [1,2].

Encapsulating or attaching a therapeutic to an engineered drug delivery carrier can improve the safety and efficacy of a drug, thus enabling new and improved therapies [3–5]. However, the translation of engineered multifunctional drug delivery vehicles from *in vitro* to the preclinical and finally the clinical setting has proven to be a considerable challenge. A reason for this are the difficulties associated with predicting the behavior of an engineered carrier in a system as complex as the human body. Built up of a hierarchy of structures with functional dimensions that differ by many orders of magnitude, the human body is a multi-level, feedback-regulated compartmentalized system, both highly dynamic and interconnected. For example, receptor–ligand

* Corresponding author. Tel.: +61 3 83443461.
E-mail address: fcaruso@unimelb.edu.au (F. Caruso).

http://dx.doi.org/10.1016/j.jconrel.2014.04.030
0168-3659/

interactions at the nanometer scale can cause the release and distribution of hormones that can, ultimately, lead to organism-level changes. To work at, and understand, all of these length scales, especially at the smallest dimensions, requires a highly interdisciplinary approach [6].

In this review, we discuss current challenges facing particle-based drug delivery systems and review strategies where microfluidic technologies have been used to address some of these issues. We provide an overview of both the production and evaluation of drug delivery particles, with a focus on microfluidics as an enabling technology. Emphasis is placed on how microfluidics can complement existing technologies by providing new ways to reliably and reproducibly engineer drug delivery particles and new *in vitro* models that can mimic important aspects of the *in vivo* situation. These features of microfluidic technologies that enable detailed analysis of mechanisms that govern interactions of particles with biological systems can facilitate the correlation of studies between *in vitro* and *in vivo*. Additionally, we provide an outlook of this growing interface between drug delivery and microfluidics, as well as discuss the impact of the evolution within microfluidics, from highly specialized "home-built" systems to easily accessible "off-the-shelf" instruments. This increase in accessibility is facilitating interdisciplinary work, thus accelerating the development of new and improved rationally designed drug delivery particles.

2. Drug delivery particles and challenges ahead

The objective of a drug delivery particle is to deliver a therapeutic to where it is needed, when it is needed. The archetypical example is to selectively deliver a cytotoxic compound to a tumor, at a high enough concentration and for long enough to kill the tumor, while at the same time leaving healthy tissue unharmed. A drug delivery particle can provide a different means toward realizing this, including: (i) facilitating formulation of the therapeutics; (ii) increasing specificity; and (iii) providing controlled release (Fig. 1). Multifunctional drug delivery particles therefore have the potential to enable the use of new drugs as well as to improve the performance of existing drugs.

Despite the great promise of drug delivery, significant challenges still remain. Today, several particle-based drug delivery systems exist in the clinic and others are currently undergoing clinical trials [7–9]. However, these successes should be considered against a backdrop of many different research groups around the world that have developed a plethora of diverse drug delivery systems, and have proven effective in *in vitro* studies with only a very few having made it successfully past preclinical studies. A reason for this is the common discrepancy seen when comparing preclinical and clinical data, where remarkable advantages in efficacy for drug carriers seen preclinically almost completely disappear when moving to humans [10], although there are examples of successful preclinical–clinical correlations [11]. This discrepancy indicates the difficulty of extracting predictive information of drug carrier behavior and performance in the clinical setting using conventional models, information that is critical for the rational design and development of drug carriers.

It may be instructive to compare this situation to the pharmaceutical industry as a whole, which is facing unprecedented challenges due to a combination of scientific, economic and legal reasons, in what has been called the "pharmaceutical industry's grand challenge" [12,13]. A main reason for this is the high rate of expensive late-phase drug attritions, and therefore a key objective is to identify and eliminate unsuccessful drugs as early as possible. Part of the solution, as proposed by four major pharmaceutical companies, could be the development and increased usage of new and improved *in vitro* pharmacological profiling assays that can provide more accurate predictions of clinical performance [14]. Reliable *in vitro* assays with high predictive power of drug-performance in humans would not only prove valuable in preclinical evaluation, but could also inform and guide the initial research and development of new therapeutics.

To apply this to the field of drug delivery, several other factors need to be considered when evaluating engineered particles, in addition to the characteristics of the therapeutic to be delivered. Important factors affecting the behavior of drug delivery particles in a biological system include both physicochemical parameters of the particles as well as characteristics of the biological target environment [15–20]. Further,

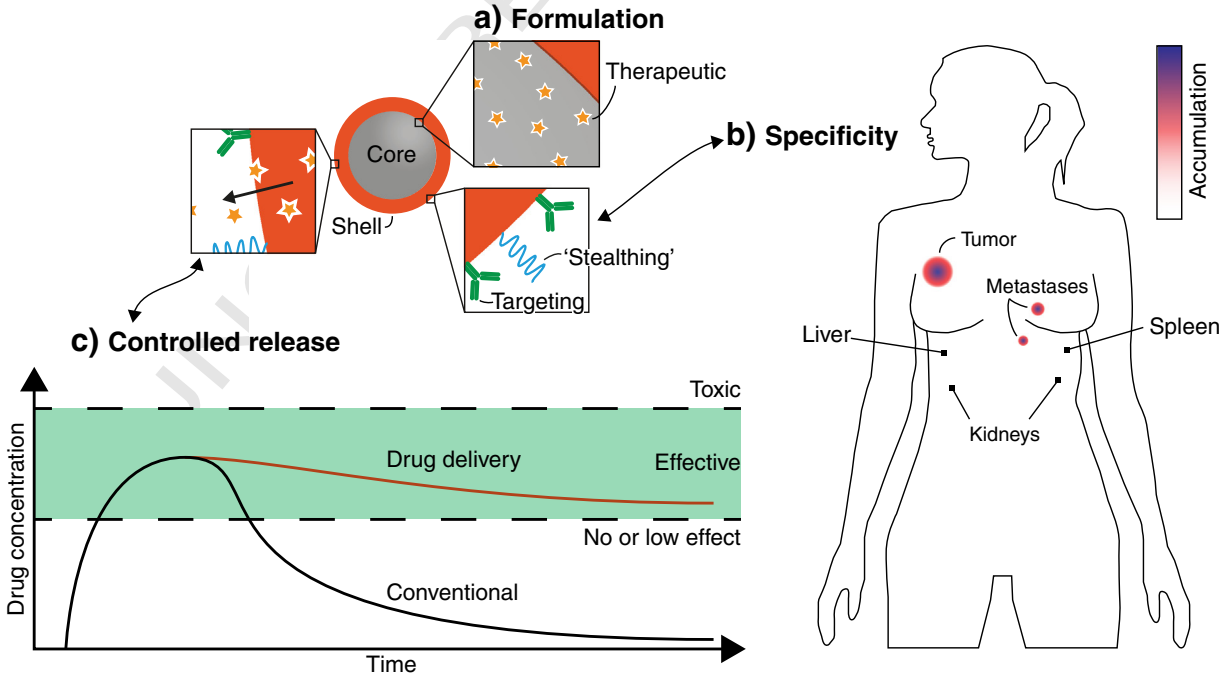

Fig. 1. Objectives for drug delivery particles, for example a core-shell nanoparticle. a) Facilitate the formulation of the therapeutic through engineered materials, for example by encapsulating a hydrophobic drug inside a hydrophilic shell. b) Increase the specificity of a drug, for example through the use of targeting and "stealthing" ligands. Ideally free drug should be released only at the intended site of action (*e.g.*, tumor site for cancer drugs) with minimal accumulation at non-target sites, typically including the spleen, the liver and the kidneys. c) Provide control over drug release kinetics, for example to keep the concentration of a drug within the therapeutic window for prolonged periods of time.

Please cite this article as: M. Björnmalm, et al., Engineering and evaluating drug delivery particles in microfluidic devices, J. Control. Release (2014), http://dx.doi.org/10.1016/j.jconrel.2014.04.030