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Multiphase microfluidic synthesis of micro- and nanostructures for pharmaceutical applications

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HIGHLIGHTS

- Multiphase microfluidics for the synthesis of micro-/nanostructures is presented.
- Development of carriers with multiple functionalities and components is discussed.
- Utilization of microfluidics towards developing biomimetic chips is highlighted.
- Special emphasis is on tumor-on-a-chip and organs-on-a-chip for carriers evaluation.

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ABSTRACT

Multiphase microfluidics has attracted significant interest in making micro- and nanostructures for various applications because of its capabilities in precisely controlling and manipulating a small volume of liquids. In this review, we introduce the recent advances in making micro- and nanostructures for pharmaceutical applications, including microparticles and microcapsules for controlled release, nanoparticles for drug delivery and microgels for 3D cell culture. With the development of more advanced microfluidic systems, the research focus in this field has shifted from making simple micro- and nanostructures to multifunctional systems to achieve more desirable functions. However, these multifunctions may lose their advantages that have been demonstrated *in vitro* once they are applied *in vivo* or later in human. The key challenge is a lack of fundamental understanding of the interactions between the micro- and nanomaterials and the biology systems. Consequently, the translation of these advanced materials lags far behind their extensive laboratory research. To better understand the micro- or nano-bio interactions, the development of new *in vivo*-mimicking models is imperative. Microfluidics has demonstrated its great potential in creating physiologically relevant models including 3D cell culture, tumor-on-a-chip and organs-on-a-chip. Therefore, efforts towards developing 3D cell culture and biomimetic chips including tumor-on-a-chip and organs-on-chips for faster and reliable evaluation of these micro- and nanosystems are also highlighted.

1. Introduction

There has been a long-standing need for improved pharmaceutical formulations that are capable of delivering therapeutics (drugs, genes, and biomolecules) at a controllable rate to specific sites (cell, tissue or organ). Novel carriers hold great promise in achieving enhanced bioavailability, reduced cytotoxicity, targeted delivery, controlled release, and improved efficacy that can ultimately result in desired therapeutic responses in the body. Among these carriers, micro- (Kurmi et al., 2010; Leong and Wang, 2015; Skorb and Möhwald, 2014) and nano- (Gref et al., 2012; Peer et al., 2007; Schroeder et al., 2010; Wang et al., 2012) structures have attracted significant research interest because of their tunability in physical (size, structures, porosity, and mechanical strength) and chemical (compositions, reactivity, biocompatibility, and biodegradability) properties, and flexibility in integrating different functions, such as for active/passive targeting, stimuli-responsive release, and diagnostics/imaging. To enable their full potential in practical pharmaceutical applications, the development of advanced and robust platform technologies for the manufacture of micro- and nanostructured materials with high degree of uniformity (size, size distribution, and shape), batch-to-batch reproducibility and scale-up possibilities, becomes highly essential.

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Microfluidics as modern technology has been transforming some of the industrial practices for controllable synthesis of multi-component carrier systems with sophisticated structures and multiple functions (Riahi et al., 2015; Vladisavljevic et al., 2013). Multiphase microfluidics involves two or more partially or immiscible fluids in contact. It has been commonly applied to enhance mixing, increase mass transfer across phase boundaries, and reduce dispersion (Günther and Jensen, 2007; Zhao and Middelberg, 2011). Also, microfluidics has unique characteristics such as pico- to nanoliters of reagents, nano- to microseconds of mixing, reaction and self-assembly, real-time monitoring/imaging and direct scale-out. These properties offer significant advantages for relatively low-cost and high-throughput production of micro- (microparticles, microcapsules, and microgels) (Gañán-Calvo et al., 2013; Shim et al., 2013; Zhao, 2013) and nanocarriers (polymeric nanoparticles, liposomes, and hybrid nanoparticles) (Khan et al., 2015b; Zhao et al., 2011).

Despite the vast amount of efforts in developing various micro-/nano-carriers, their translation from *in vitro* to animal studies (preclinical) and finally human trials (clinical) has been tremendously expensive with long timelines and quite often fails at the later stage of their development even after entering human clinical trials. Until now, only a few nanosystems have been approved by the U.S. Food and Drug Administration (FDA) for human use, for example, Doxil (a liposomal formulation encapsulating Doxorubicin) (Koynova and Tenchov, 2015) and Abraxane (based on the nanoparticle albumin-bound (nab) technology to deliver Paclitaxel) (Qiang et al., 2009) for cancer treatments. One of the hurdles is the lack of robust *in vitro* or *in vivo* systems that can predict the behavior of drugs and carriers in the human body. *In vivo* animal models have been widely used but cannot accurately predict human responses due to inter-species differences. Also, animal experiments are time-consuming, high cost, and have ethical concerns. Microfluidics offers structures and networks at the micrometer length scale comparable to relevant physiological length scales and can incorporate fluid flows and mechanical forces capable of mimicking the *in vivo* microenvironment. Therefore, it enables the investigation of complex interactions between these micro-/nanosystems and biological systems. Furthermore, integration of tumor spheroids or organoids with microfluidics to build tumor-on-a-chip, organs-on-a-chip, and ultimately human body-on-a-chip creates a platform that cannot be achieved by conventional cell and tissue culture in well plates. Thus, organs-on-a-chip can be useful for predicting preclinical and even clinical performances of new therapeutics and micro-/nano-delivery vehicles at early stages of drug development.

In this review, we will critically review the recent advances in making micro- (microparticles, microcapsules, and microgels) and nanostructures (polymeric, liposomes, and hybrid nanoparticles) in microfluidics for therapeutic delivery and controlled release, with a focus on new structures, new functions, and their pharmaceutical applications. We will also highlight recent development in making microgels for 3D cell culture as well as tumor-on-a-chip and organs-on-a-chip, which provide rapid and reliable screening and evaluation tools for accelerating the development of drug delivery systems.

2. Well-controlled synthesis of micro- and nanostructures and their pharmaceutical applications

A wide variety of micro- and nanostructures have been synthesized using microfluidics (Fig. 1), including microparticles, microcapsules, microgels, and nanoparticles made of various materials including synthetic polymers, natural polymers, lipids, and hybrid materials. This section will introduce the synthesis of these micro- and nanostructures and their pharmaceutical applications.

2.1. Synthesis of microstructures and their applications

2.1.1. Microparticles

Microparticles herein are defined as particles with a size ranging from 1 to 1000 μm. Microfluidics offers several unique advantages for preparing microparticles, such as precise control over particle size, surface morphology, and high flexibility in making microparticles with various materials and different structures.

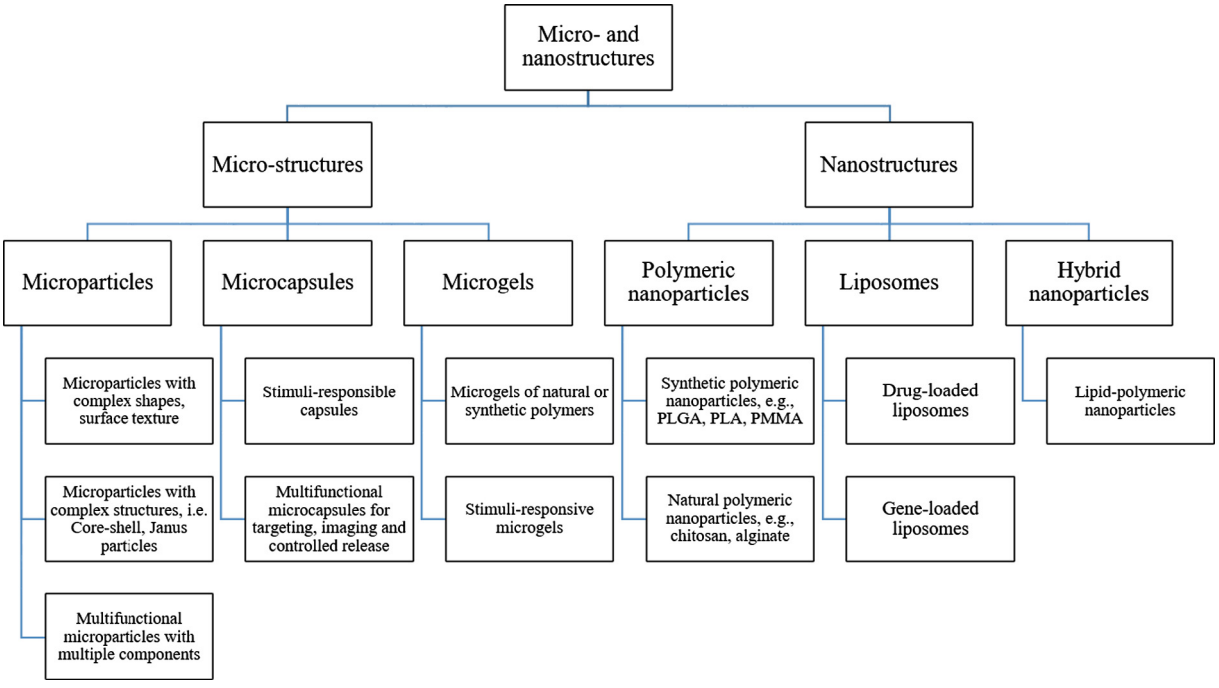

Fig. 1. Types of micro- and nanostructures synthesized using microfluidics.