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3D lithographically fabricated nanoliter containers for drug delivery

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Abstract

Lithographic patterning offers the possibility for precise structuring of drug delivery devices. The fabrication process can also facilitate the incorporation of advanced functionality for imaging, sensing, telemetry and actuation. However, a major limitation of present day lithographic fabrication is the inherent two-dimensionality of the patterning process. We review a new approach to construct three dimensional (3D) patterned containers by lithographically patterning two dimensional (2D) templates with liquefiable hinges that spontaneously fold upon heating into hollow polyhedral containers. The containers have finite encapsulation volumes, can be made small enough to pass through a hypodermic needle, and the 3D profile of the containers facilitates enhanced diffusion with the surrounding medium as compared to reservoir systems fabricated in planar substrates. We compare the features of the containers to those of present day drug delivery systems. These features include ease of manufacture, versatility in size and shape, monodisperse porosity, ability for spatial manipulation and remote triggering to release drugs on-demand, the incorporation of electronic modules, cell encapsulation, biocompatibility and stability. We also review possible applications in drug delivery and cell encapsulation therapy (CET). The results summarized in this review suggest a new strategy to enable construction of "smart", three dimensional drug delivery systems using lithography.

Keywords: Drug delivery; Lithography; Cell encapsulation; On-demand release; Self-assembly; Containers

Contents

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1. Introduction

Drug delivery systems are evolving from oral pills with systemic effects, to miniaturized targeted devices with high spatial and temporal control over drug release kinetics. Spatial control allows for high anatomic specificity, lower dosage, and decreased side effects. Temporal control of drug release allows for sustained dosing and minimized fluctuations from the therapeutic window. Most miniaturized drug delivery systems are based on either organic materials such as polymers, gels, vesicles, and liposomes or inorganic metallic and semiconducting nanoparticles. Organic systems such as polymeric particles and films have been approved for use in oral, implantable, injectable, inhalable, or patch form and these have allowed new sustained release treatments to come to market [1]. In cancer therapies, liposomes encapsulating novel drug molecules such as small interfering RNA have been used to target surface receptors specific to cancer cells [2]. Existing sustained release polymeric systems [3] can also be placed locally to provide higher cytotoxic concentrations near tumor sites for increased specificity of drug action. In contrast to organic materials, metallic and semiconducting materials have novel optical and electronic properties. Hence, metallic nanoparticles can be used to ablate cancer cells by heating with near infrared light [4]. In addition, cells, gels or polymers loaded with magnetic particles can be tracked using magnetic resonance (MR) imaging [5] and heated by remote magnetic fields [6]. Semiconducting quantum dots have been used as fluorescent probes to image tumors and the lymphatic system of animals [7,8].

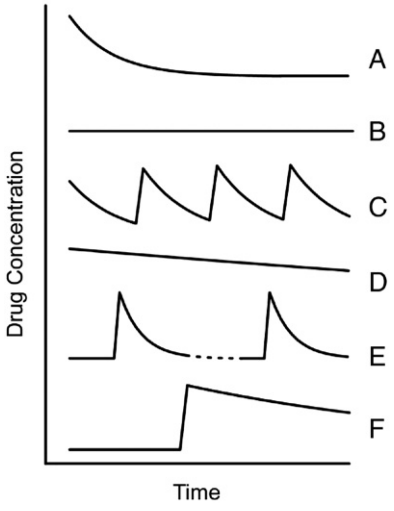

Fig. 1. Idealized drug release profiles from several methods of administration. (A) Single oral dose. (B) Continuous infusion. (C) Repeated oral dosing. (D) Sustained release formulation, no initial spike. Two new profiles are achievable by lithographically fabricated remote release devices. (E) Container releasing drugs on-demand. (F) Container loaded with a controlled release polymer; release is triggered on-demand followed by sustained release.

The next generation of drug delivery systems, in addition to having spatial and temporal control described above, is expected to be "smart" and enable therapy that is responsive to the patient's needs. As with present day modalities, dosage would be predictable and standardized. Additionally, these advanced systems would protect drugs from environmental or biological degradation in the body and use closed loop control to assist the patient with homeostasis and allow for autonomous drug administration. Mechanisms for facilitating feedback necessitate the incorporation of advanced functional modules such as sensors, memory and logic devices, directly onto a drug delivery device. One possible example is the delivery of insulin autonomously, in response to changing glucose levels. Alternatively, one may desire to duplicate natural developmental pathways to direct growth of nerves, blood vessels, tissues and organs by delivering specific growth hormones at precise times, possibly anisotropically, in order to fully program developing tissue [9]. As compared to typical present day drug release profiles (Fig. 1A–D), it is anticipated that on-demand release (Fig. 1E–F) would be enabled by remote communication or autonomous logic.

Realizing these goals for "smart" drug delivery systems requires the development of small independent reservoir structures or containers that can be manufactured inexpensively, loaded easily with drugs, delivered with minimal trauma, and be easily tracked, programmed or controlled. Small containers would also allow for precise spatial positioning of drug release [10]. The ideal device should be small enough to be swallowed or injected, as these modalities are in widespread use and well-tolerated by patients. Many of these characteristics, especially advanced electronic functionality, can only be achieved in drug delivery systems if lithographic methods are utilized to fabricate drug delivery systems.

2. Lithographically fabricated drug delivery systems

Lithographic fabrication provides a mature set of tools that allow for patterning substrates at the nanometer to millimeter scale; it allows microelectronic devices and microelectromechanical systems (MEMS) to be fabricated in large numbers on silicon wafer substrates. Lithographic microfabrication is a key technology that has enabled the fabrication of a wide range of miniaturized devices for computation, memory storage, wireless communication, remote sensing and high fidelity imaging [11–13]. The most widely used lithographic fabrication techniques include optical and electron beam lithography, microcontact printing, selective etching and thin film deposition. Lithographic fabrication can also be applied to a large variety of materials