Advanced Drug Delivery Reviews 108 (2017) 68–82

Contents lists available at ScienceDirect

Advanced Drug Delivery Reviews

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

Mechanoresponsive materials for drug delivery: Harnessing forces for controlled release☆

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ARTICLE INFO

Article history:
Received 17 September 2016
Received in revised form 1 November 2016
Accepted 9 November 2016
Available online 14 November 2016

Keywords:
Drug delivery
Compression
Tension
Shear
Biomaterials
Nanomaterials

ABSTRACT

Mechanically-activated delivery systems harness existing physiological and/or externally-applied forces to provide spatiotemporal control over the release of active agents. Current strategies to deliver therapeutic proteins and drugs use three types of mechanical stimuli: compression, tension, and shear. Based on the intended application, each stimulus requires specific material selection, in terms of substrate composition and size (*e.g.*, macrostructured materials and nanomaterials), for optimal *in vitro* and *in vivo* performance. For example, compressive systems typically utilize hydrogels or elastomeric substrates that respond to and withstand cyclic compressive loading, whereas, tension-responsive systems use composites to compartmentalize payloads. Finally, shear-activated systems are based on nanoassemblies or microaggregates that respond to physiological or externally-applied shear stresses. In order to provide a comprehensive assessment of current research on mechanoresponsive drug delivery, the mechanical stimuli intrinsically present in the human body are first discussed, along with the mechanical forces typically applied during medical device interventions, followed by in-depth descriptions of compression, tension, and shear-mediated drug delivery devices. We conclude by summarizing the progress of current research aimed at integrating mechanoresponsive elements within these devices, identifying additional clinical opportunities for mechanically-activated systems, and discussing future prospects.

Contents

☆ This review is part of the *Advanced Drug Delivery Reviews* theme issue on "Editors' Collection 2016".

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http://dx.doi.org/10.1016/j.addr.2016.11.001
0169-409X/

1. Introduction

The delivery of therapeutic agents to a specific location with optimal dose and duration remains a significant clinical challenge. This multifaceted problem is being investigated using a myriad of drug delivery strategies because systemic drug administration—although widely used in the clinic—typically requires multiple doses to treat diseased tissue. However, this leads to significant and widespread off-target side effects due to exposure of healthy tissue. Stimuli-responsive materials are well-suited for applications in drug delivery, actively releasing their drug payloads in response to either physiological or externally-applied triggers. This spatiotemporal control over drug release is widely demonstrated for stimuli such as: pH [1–11], temperature [1,9,10,12–21], light [22–26], ionic strength [27–29], electrical potential [30–37], and applied magnetic fields [38–48]. While some of these systems ultimately undergo a mechanical change, such as deformation, swelling, or change in modulus (*i.e.*, when temperatures reach above the lower critical solution temperature or below the upper critical solution temperature), they will not be discussed as these systems are previously reviewed. Instead, this review highlights recent exciting breakthroughs with stimuli-responsive systems that respond directly to mechanical forces and summarizes pioneering reports that have launched the field.

Mechanically-activated systems are triggered by mechanical forces in the body that either occur physiologically or are exerted on the body by external devices, both over a wide magnitude (Fig. 1). Generally, an unopposed force exerted on an object accelerates its motion. The distribution of the force on the object is described as the mechanical stress, which can result in deformation. Microscopic cellular forces [49–54] are present and coordinate into macroscopic forces for processes such as wound repair and inflammation. Further coordination results in the exertion of even greater forces by various systems, such as the musculoskeletal [55,56], cardiovascular [57–59], and respiratory systems [60,61]. Alternatively, external triggers are applied by medical devices such as stents [62–65] and catheters [66,67] that mechanically open blocked or narrowed structures, or are applied by another user or self-exerted to control administration. Therefore, drug and protein delivery systems that respond to mechanical forces serve as innovative solutions to control on-demand release within a physiological environment. Designing such mechanoresponsive systems that account for the dynamic nature of the human body will bring about novel solutions to clinical challenges.

Mechanical stimuli are quantified by force and displacement (Fig. 2). In compression, a force is applied, resulting in an equal but opposing force along the same axis, generally reducing the object's length along that direction. Similarly, an object under tension is pulled or stretched, lengthening the object along the axis. This force, and resulting deformation, can be converted into stress and strain. For engineering stress (σ), the force is normalized by the cross sectional area while engineering strain (ε) calculates the relative change in displacement — the difference in length divided by the original length. Instead of applying forces normal to the cross section, shear forces are applied parallel to the object's cross section. Shear stress is similarly defined as the parallel force divided by the cross sectional area acted upon; shear strain is the strain in the parallel direction. The overall elastic material property is expressed by Young's modulus: $E = stress / strain$. The shear modulus is defined as $G = E / (2(1 + \nu))$, where ν is Poisson's ratio, which describes the expansion of the material along the axis compared to the compression perpendicular to the axis.

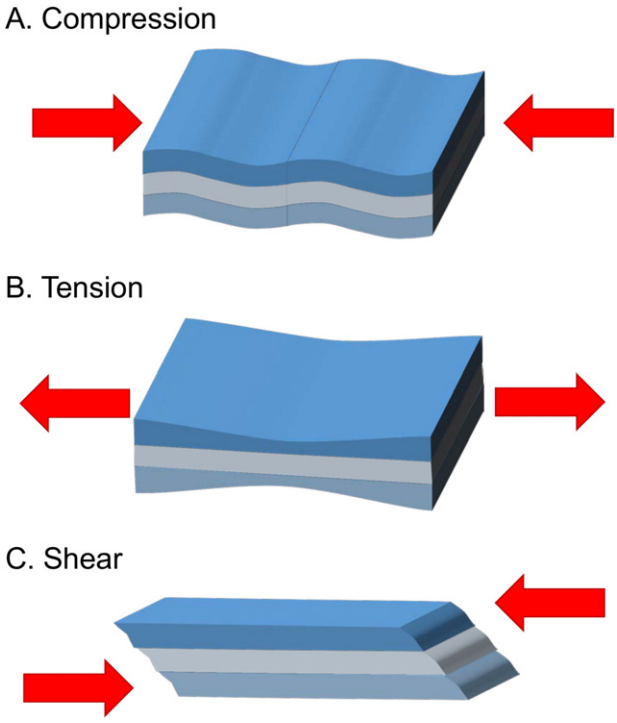

Fig. 2. Schematic representation of compressive, tensile, and shear forces.

While there are relatively few reports of mechanoresponsive drug delivery systems [68], they cover the breadth of mechanical forces: compression, tension, and shear. Mechanoresponsive drug delivery is attractive due to the ease of applying compressive, tensile, and shear stimuli, and to the ubiquity of these forces in the human body. While ultrasound is also considered a mechanical stimulus, several recent reviews have been published on ultrasound-triggered drug delivery [69–83], and thus will not be discussed here. The scope of the current review focuses on drug delivery systems that utilize compression, tension,

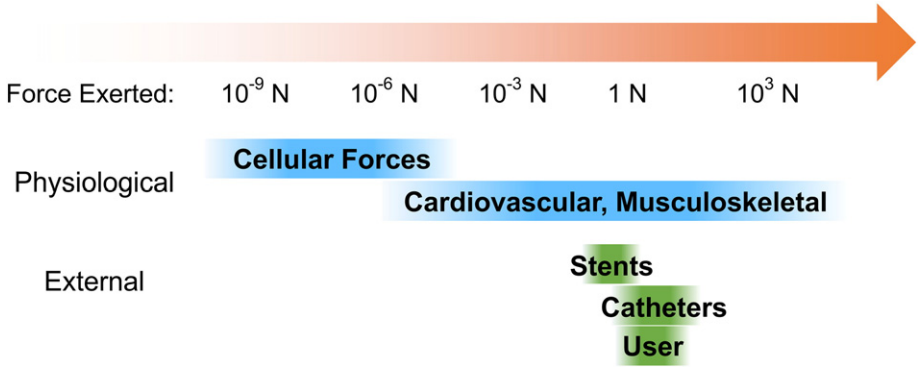

Fig. 1. Physiological and external forces and their relative magnitudes present in the body.