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Impact of particle elasticity on particle-based drug delivery systems☆

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ABSTRACT

Modification of nano/micro-particle physical parameters (e.g. size, shape, surface charge) has proven to be an effective method to enhance their delivery abilities. Recently, advances in particle synthesis have facilitated investigations into the role that particle elasticity plays in modulating drug delivery processes. This review will highlight: (i) methods to tune particle elasticity, (ii) the role particle elasticity plays in cellular internalization, (iii) the role of particle elasticity in modulating circulation times, (iv) the effect of particle elasticity on altering biodistribution and tissue targeting, and (v) the application of computational methods to explain the differences in cellular internalization of particles of different elasticities. Overall, literature reports suggest a complex relationship between particle elasticity and drug delivery processes. Despite this complex relationship, it is clear from numerous in vitro and in vivo studies that particle elasticity is an important parameter that can be leveraged to improve blood circulation, tissue targeting, and specific interactions with cells.

Contents

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1. Introduction

The physical properties of nano/micro-particles can be modified to dramatically alter their biological function and fate [1–5]. This is especially advantageous when developing nano/micro-particle drug delivery systems, as these modifications can facilitate the design of nano/micro-particles capable of performing highly specific functions such as long circulation and specific targeting to diseased tissues [6–10]. The effect that size [11], shape [12,13], surface charge [14,15] and hydrophobicity [7,16,17] have on the delivery abilities of particles is well known since advances in particle synthesis [18–20] have facilitated systematic studies that investigate their influence on drug delivery. Despite these advances very few studies have postulated [21,22], or exclusively examined, the role that elasticity plays in particle drug delivery, even though the role of material elasticity is well known in other fields, especially tissue engineering [23–25].

This review will focus on the role that nano/micro-particle elasticity plays in particle-based drug delivery and how elasticity can be leveraged to tune the biological function and fate of nano/micro-particles. Specifically, methods to tune particle elasticity will be highlighted and discussed. The role of elasticity in controlling particle blood circulation, tissue targeting, and cellular interactions (e.g. endothelial, cancer and immune cells) will be highlighted. Furthermore, the impact of particle elasticity on transcytosis, biodegradability and biocompatibility, and targeting under flow will be discussed. Detailed discussions on the effect of other nano/micro-particle modifications, such as size, shape, surface charge, or hydrophobicity are beyond the scope of this review article, as they have been extensively reviewed elsewhere [7,10–12,16,17]. Furthermore, the role of substrate elasticity in directing stem cell fate [23–27] is also outside the scope of this review although those studies, in many ways, have inspired investigations of the role of particle elasticity in drug delivery.

2. Elasticity definitions, terms, and usage

Terms including: elasticity, plasticity, hardness, softness, shear modulus, bulk modulus, elastic modulus, stiffness, flexibility, rigidity, Young's modulus, toughness, malleability, and ductility are widely used in the literature when describing material properties. However, often unaddressed is that each of these terms describes a unique physical parameter. In fact, many of these parameters are measured by different techniques and are represented by different units. Thus, comparing the values reported between studies is not straightforward and in many cases not appropriate. Of particular interest for nano/micro-particles are stiffness and elasticity, including the various elastic moduli (Table 1). Elasticity is defined as a material's ability to resist deformation while under *stress* (e.g. shear, uniaxial or bulk stresses) and subsequently return to its original size/shape (Table 1). Stiffness, complementary to flexibility, is defined as a material's ability to resist deformation while undergoing an applied *force* (Table 1). The main difference between the two is that elasticity is an intrinsic property that applies to the material, while stiffness is an extensive property that considers the geometry (e.g. size and shape) of the material. For this article, direct comparisons between particles will make use of the colloquial terms “soft” and “hard”. Furthermore, specific elasticity or stiffness values between studies will not be directly compared; instead, particular focus will be on general discussions aimed at elucidating the fundamental differences soft and hard nanoparticles exhibit in drug delivery processes. Abbreviations will be used throughout the manuscript to highlight the specific moduli reported: (B) for bulk modulus, (Y) for Young's modulus, and (S) for shear modulus.

3. Methods to control nanoparticle elasticity

A variety of methods can be used to tune nanoparticle elasticity, however, the majority of research investigating the role of elasticity in particulate drug delivery has leveraged the use of either colloidal hydrogels or layer-by-layer/templated capsules [21,28]. We would like to point out that other particle types, notably core–shell particles containing a solid polymeric core inside of a lipid shell [29,30] and cylindrical polymer brushes [31], can be used to investigate and tune particle elasticity exist. These systems have yet to be explored in as much depth as hydrogels or LbL particles and as such their synthesis will not be covered here in detail; however, their specific use in drug delivery applications and their contributions towards fundamental particle elasticity studies will be covered in the later sections. Here, we will highlight how hydrogels and layer-by-layer/templated capsules facilitate synthesis of otherwise physicochemically identical particles over a range of elasticities, with particular emphasis on particles that have been utilized for drug delivery applications.

3.1. Hydrogel particles

Hydrogels are networks of hydrophilic polymer chains that can be tailored to have various physical properties and take the form of macroscopic materials or colloidal suspensions (Fig. 1a) [32–34]. By virtue of being hydrophilic and porous, hydrogels predominately consist of water and thus by regulating their fluid content via modifications to internal structure, it is straightforward to tune their elasticity [35–37]. Varying the cross-linking density (Fig. 1b) is a well-established method for controlling hydrogel elasticity [36], and as such is a commonly used method. However, depending on the extent of crosslinker used, changes to additional properties may occur [36], so care must be taken to ensure accurate comparisons between particles of different elasticities. Using this method, 2-hydroxyethyl acrylate (HEA) red blood cell sized and shaped hydrogels were synthesized using the PRINT® process under varying amounts of cross-linking densities, which tuned particle bulk moduli from 7.8 to 63.9 kPa [20]. Varying cross-linking density has also been used in combination with emulsion methods to make poly(carboxybetaine) (pCB) nanogels (~120 nm) of bulk moduli ranging from 180 to 1350 kPa [38], N,N-diethyl acrylamide (DEA) and 2-hydroxyethyl methacrylate hydrogel particles (~170 nm) of Young's moduli ranging from 18 to 211 kPa [39], and poly(2-hydroxyethyl methacrylate) (HEMA) hydrogel particles (900–1300 nm) of bulk moduli ranging from 16.7 to 155.7 kPa (Fig. 1c) [40]. More recently, a method varying the amount of polymer added during synthesis was used to control particle elasticity by directly controlling the final polymer

Table 1
Elasticity, stiffness and moduli definitions.

Physical parameter	Definition	Units
Stiffness (complementary to flexibility)	• Structure property: extensive • Ability to resist distorting force • Depends on material and geometry	Newtons per meter
Elasticity	• Material property: intrinsic • Ability to resist distorting stress • Depends on material	N/A
Young's/elastic modulus (Y)	• Material property: intrinsic • Response to uniaxial stress • Resistance to stretching • Depends on material	Pascals
Bulk modulus (B)	• Material property: intrinsic • Response to uniform pressure • Resistance to compression • Depends on material	Pascals
Shear modulus (S)	• Material property: intrinsic • Response to shear • Depends on material	Pascals