

Roles of Nanoparticle Properties in Nanotechnology for Medical Therapeutics

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Abstract. Nanotechnology-based therapeutics have attracted a great deal of attention to overcome the lack of specificity and permeability of conventional agents. The unusual physicochemical properties of nanoparticles make therapeutics at the nanoscale possible. More recently, the enhanced understanding of these properties has led to the rapid development of nanotechnology for various nano-based treatments. Herein, the basics of nanoparticle physicochemical properties, emphasizing optical, surface, and mechanical properties, are presented. Meanwhile, the current and emerging nanotechnologies in the field of medical therapeutics of the past decade are discussed, with a special emphasis on the underlying mechanisms of these properties in these applications. However, these properties' roles in nano-based therapeutics have just begun, and further exploration of how nanoparticle properties affect cell-nanoparticle interactions is necessary. Therefore, the interesting studies and findings surveyed in this review will provide a better understanding of how this area has evolved over the past decades, and the fundamental understanding of nanoparticle properties will shed light on designing and exploring better nanotechnologies for medical treatments.

Keywords: Nanotechnology, Medical Therapeutics, Optical Properties, Mechanical Properties, Chemical Properties.

1. Introduction

The properties of nanoparticles are the reason for the wide range of nanotechnology applications in medical therapeutics, from imaging to gene therapy to drug delivery [1]. The first concerns size, where nanoparticles can be synthesized in controlled sizes, enabling them to be compared to living organisms, from viruses (10-150nm), genes (2nm) to proteins (3-50nm) [2]. In this way, they are not easily recognized by the immune system in the body and can cross biological barriers, thus contributing to site-specific targeting for the cure of different diseases [1, 3]. Different sizes have different surface-to-volume ratios, and the large surface-to-volume ratio of nanoparticles is a key factor in generating new physical, chemical, and mechanical properties compared to the corresponding bulk materials [2]. In sensing and therapy, physical properties include optical, electrical, and magnetic properties [2, 4-6]. An example of chemical properties is the speed of chemical reactions, in drug carriers such as liposomes, cubosomes, hexosomes, or dendrimers for targeting tumors [7, 8]. Examples of mechanical properties are softness and stiffness, which are used to modulate their biological properties [9]. In light of these, the unique properties provide a new dimension in the ability to control organisms and clinically treat diseases.

Nanotechnology is the ability to systematically arrange and manipulate the properties of matter at the atomic and molecular levels [10], to assemble and form larger structures, including devices, structures, and systems with unique functions on the 1-100nm scale [11, 12]. The most complex arrangements of matter that we know of are those of living entities and organs [9]. The function of living organisms depends on specific forms of matter on all the various length scales, and many of the biological particles involved are in the nanometer range in size, such as red blood cells, enzymes, and viruses [10, 11]. Their internal workings also occur naturally on the nanoscale [13]. In this sense, nanotechnology is natural in pharmaceuticals. To compete with the same bulk materials, the unique properties of nanoparticles, as their higher surface-to-volume ratio, allow them to bind, absorb and transport small biomolecules, such as drug RNA, proteins, and other molecules, to the target site,

thereby increasing the efficacy of therapeutic agents. Thus, developing new and effective medical treatments will be one of the greatest values of nanotechnology [14].

This assay carries out a search for publications about the roles of physicochemical properties of nanoparticles in nanotechnology applied in the field of medical therapeutics in PubMed database sorted by best match from 2000 to 2022, and it is formatted in the following way. First, the basis of nanoparticles' optical, surface, and mechanical properties is presented in detail, differing in important ways from the properties of bulk materials, single atoms, and molecules. After that, it highlights how these properties affect several biological interactions, including blood circulation, cell uptake, and internalization. Furthermore, the roles of these properties in nanotechnologies for the application of medical treatments are investigated. Therefore, this will help understand the relationship between nanoparticles properties and biological processes as well as these relevant therapeutic applications, then designing optimal nanotechnologies for medical therapeutics.

2. Roles of nanoparticle properties in nanotechnology for medical therapeutics

The growing understanding of the physicochemical properties of nanoparticles increases the potential for nanotechnology to engage with the human internal environment, which implies therapeutic applications for humans. Nanoparticles enter a biological system, then react upon contact with proteins, cells, tissues, or organs to create a range of nanoparticle/biological interfaces that are determined by the properties of the nanoparticles. These interactions also lead to the formation of protein coronas, particle wrapping, and intracellular uptake processes in either biocompatible or bioadverse results [15]. In this section, the role of the surface, optics, and mechanical properties have been studied in the PubMed database from 2000 to 2022 in order of best fit. It includes 1) the basic terminologies of these nanoparticles' properties; 2) these properties' roles in biological processes; 3) current advancements in nanotechnologies for medical therapeutics, with a special emphasis on the underlying mechanisms of these properties in these applications.

2.1. Optical properties

Optical properties describe the interaction of radiation with matter in physics. When light impinges upon nanoparticles, various processes can occur. Among these, light being absorbed or re-emitted, like fluorescence [16], or scattered at the same frequency as the incoming light, such as Mie or Rayleigh scattering and surface-enhanced spectroscopy, have been widely explored in the nanotechnology field [17-19]. Specifically, Mie presented a solution to Maxwell's equations: "extinction = scattering + absorption", describing the extinction spectra of spherical particles with arbitrary size [17]. The local electromagnetic field of the incident light can be enhanced to enhance any spectral signals from surface molecules, which means surface-enhanced spectroscopy [17, 19].

Gold nanoparticles have numerous readily polarizable conduction electrons, leading to high and tunable non-linear optical properties [20]. When exposed to light radiation, these conducting electrons at the gold nanoparticles' surface cause collective oscillation in resonance with the electromagnetic field, known as surface Plasmon resonance [17, 19]. In fact, gold nanoparticles have larger extinction cross sections compared to the same bulk material, potentially achieving 100% photothermal conversion efficiency and high photostability [20]. These characters have attracted much interest in nanotechnology and explored the applications in medical treatments, especially photothermal cancer therapy [19].

Taghizadeh et al., in 2019, reviewed gold nanoparticles applied in photothermal therapy of liver cancer treatment by taking advantage of these tunable optical properties [21]. Gold nanoparticles were first used as sensitizers in photothermal therapy in spherical structures in 2003. The mechanism is based on gold nanoparticles' vibrational effects, and the surface plasmons resonate under photoexcitation. Hence, a better absorption band for the near-infrared region can be achieved, increasing the penetration of light into targeted tissues. In this way, the local temperature up to tens or hundreds of degrees within a short time damages the targeted tumor tissues. However, the

absorption of spherical structures remains weak in the near-infrared (NIR) window of the desired tissue penetration, resulting in the undesired photothermal efficiency in the clinic. To address this issue, Wang et al. in 2019 showed aggregated gold nanoparticles, self-assembled by a biotemplate, silk fibroin [22]. This templating effect could expand and redshift light absorption towards NIR. As a result, the photothermal conversion efficiency achieved 38.42%, which was higher than that of gold nanoparticles, 28.81%, under the same 808 nm NIR irradiation. This gave a valuable relevance for an optimal choice. Furthermore, polydopamine-coated nanoparticle superstructures studied by Pan et al. (2020) also had an enhanced photothermal conversion efficiency of 33% under the same irradiation, owing to the enhanced visible-NIR absorption of these particles by a site-specifically polymerized strategy [23, 24]. In the Guglielmelli A et al. study in 2021, keratin-coated gold nanoparticles were studied as therapeutics for plasmonic photothermal therapy against cancer-related diseases, not only achieving enhanced efficiency but also the abilities of biocompatibility and cellular uptake [25]. In spite of numerous efficiency improvements, metastatic cancer would not be suppressed or eradicated by photothermal therapy. In light of these, further studies are well worth investigating in the combining therapies of photothermal and others, such as the chemo-photothermal combining therapy [26], especially in the aspects of stability enhancement, side effect reduction, tumor suppression or even eradication, in order to provide more appropriate approaches.

2.2. Surface properties

Nanoparticles used as photothermal agents in photothermal cancer therapy often require high photothermal stability. However, nanoparticles with relatively high stability usually degrade slowly or are difficult to degrade, causing potential excretion problems and biosafety issues; either that or, although they can degrade rapidly, they cannot guarantee stability, such as black phosphorus nanosheets [27]. Hu et al. designed Cu²⁺-capsulated black phosphorus nanosheets through surface electrostatic attraction to circumvent these limitations. As a result, the photothermal conversion efficiency was largely enhanced by the capsulated Cu²⁺, while still retaining the nanosheets' ability to rapid degradation. In addition, Cu²⁺ reacted with hydrogen peroxide in the tumor microenvironment to produce cytotoxic hydroxyl groups, enabling concurrent chemodynamic therapy and enhancing therapeutic efficacy.

Surface properties of nanoparticles are major factors affecting the interaction of these nanoparticles with biological systems [28]. It is known that positively charged NP interacts with negatively charged phospholipid components of cell membranes, increasing non-specific interactions with biological cells and cell toxicity. These electrostatic charge interactions are entangled with protein corona effects, in which nanoparticles are encapsulated by immune cells or other protein macromolecules, leading to non-specific interactions with cell membranes. This has been shown to increase the clearance of nanoparticles by macrophages and reduce their downstream therapeutic effects.

In order to limit these clearances, neutralized nanoparticle surface modifications, such as polyethylene glycol (PEG), are normal methods to resist undesired reactions at nanoparticles/biologicals interfaces, like protein adsorption or clearance by immune cells [29]. Unfortunately, PEG modification is not that desirable, which includes synthesis difficulties and association with immune responses. To overcome these obstacles, Rattan, R et al. neutralized silica nanocapsules' surface by acetylation, and compared with a PEGylation approach. It found that acetylation and PEGylation were comparable in reducing clearance, and neither affected the tumor-specific targeting [28]. This means that the neutralized modification method can block these unwanted non-specific aggregations of nanoparticles to modify the clearance rates, which is important for the treatments.

2.3. Mechanical properties

Mechanical properties describe the characteristics of a material when subjected to applied loads [28]. Due to nanoparticle size, surface, and quantum effect, they exhibit different mechanical

properties relative to the same bulk materials [27]. In this section, this information can be expressed in terms of how the nanoparticles behave at the nanoparticle/biological interfaces. Moreover, modulation of their mechanical properties can lead to changes in certain biological functions such as blood circulation, permeation, cellular internalization, and clearance. This is mainly inspired by many cells and even viruses [9].

Softness and hardness are becoming key parameters for regulating the interaction of nanoparticles with cells or biological microenvironments. Palomba, R. et al. (2018) studied the tendency of soft and hard discoidal polymeric nanoconstructs to internalization of specialized phagocytes extracted from rats. In this experiment, soft discoidal polymeric nanoconstructs mostly establish less than 30-second transient interactions with macrophages, reducing the likelihood of identification and internalization [29]. This means that soft nanostructures are unlikely to be cleared by immune cells, which in turn extends blood circulation time. A similar finding was also reported by Hui et al., a library of silica nanocapsules with different hardness was synthesized in this study and found that soft nanocapsules deformed and reduced cell binding and endocytosis rates than their hard counterparts, due to the forces from specific interactions and particle wrapping [30]. This may also lead to soft nanocapsules with slower elimination and shorter circulation times in the vasculature.

3. Conclusion

In the last decade, there has been a great deal of interest in the roles of nanoparticle properties in nanotechnologies for medical therapeutics. Additionally, the unique properties of nanoparticles that make them superior to conventional materials, such as better light reflection or color change, stronger or different thermal or conduction conversion, and greater chemical reactivity, have taken on a wider responsibility for developing new therapeutic modalities. This essay summarizes the basic terminologies of nanoparticles' optical, surface, and mechanical properties. Then, these properties' roles in biological systems have been demonstrated. It has also investigated how these properties affect nanotechnology and are used in medical treatments, with a special emphasis on the underlying mechanisms of these properties in these applications, such as gold nanoparticles as photothermal therapy agents in optical properties, black phosphorus modification in surface properties and silica nanocapsules as a drug delivery nanoparticles shown in mechanical properties. However, these unique properties of nanoparticles have an interdependent effect on determining their cellular uptake. Therefore, the combining effects of mechanical properties and surface or other parameters on modulating nano-biological interactions need to be studied more closely.

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