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A review of the analysis of the effects of nanoparticle morphology on intracellular drug delivery

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Abstract

Nanoparticles have been used as promising carriers for targeted and controlled drug delivery by researchers due to their unique physicochemical properties, such as size, surface charge, and especially shape. Among these parameters, the shape of nanoparticles has attracted increasing attention because it significantly affects their interactions with biological barriers, including blood vessels, cell membranes, and extracellular matrix. The aim of this study is to investigate and analyze the effects of nanoparticle shape on drug delivery efficiency and to classify related articles based on clinical and experimental findings. A comprehensive review was conducted on 30 scientific articles, from which 22 studies published between 2010 and 2025 were selected that directly investigated the role of particle shape in drug delivery systems. While spherical nanoparticles have received the most attention, recent evidence suggests that rod-shaped, disc-like, and elongated structures may provide increased circulation time, improved tumor penetration, and more controlled drug release profiles. The findings suggest that precise engineering of nanoparticle morphology, along with size variations, is crucial for optimizing drug delivery performance. Overall, controlling the shape of nanoparticles offers a powerful strategy for improving therapeutic outcomes in the treatment of cancer and other complex diseases.

Keywords: Cancer, Drug Delivery, Nanoparticles

Introduction

Nanotechnology, or the application of technology at the scale of a billionth of a meter, has presented scientists with an astonishing world unparalleled in human history. The convergence of nanotechnology and biotechnology, if it is carried out in a certain order, can create new tools. The biomedical applications of nanotechnology are a direct product of such convergence. The impact of nanotechnology on biomedicine refers to the development of materials and instruments designed to interact with the body at subcellular levels with a high degree of precision, which will potentially be able to enter target cells and increase therapeutic effects and reduce side effects [7].

❖ The role of physicochemical properties

Due to their small size and biocompatibility, nanoparticles are not recognized by the body's defense system as foreign

particles. Nanoparticles enable targeted drug delivery, reduce drug consumption, and enhance therapeutic effects; in addition, nanoparticles are also known as DNA and gene carriers.

In drug delivery by nanoparticles, physicochemical properties play a key role. These properties determine how the nanoparticle interacts with the cell membrane, serum proteins, and the environment, and ultimately how effective the drug entry and release pathway are [10].

We will discuss the external characteristics of nanoparticles used in drug delivery in the sections that follow:

❖ Size

Nanoparticles smaller than 200 nm usually enter cells via endocytosis, Macrophages are more likely to absorb bigger

particles. Optimal size can increase circulation time and improve penetration into target tissue (e.g., tumors). Very small particles (<10 nm) may be rapidly excreted by the kidney.

The size of nanoparticles has been the subject of numerous investigations. In the broader strategy of vascular targeting, particles are carried by the bloodstream and interact with blood vessel walls in a specific way (ligand-receptor bond formation) and a non-specific way (van der Waals, electrostatic, and steric interactions) to look for the sick endothelium (vascular target). Particles stick when the proper circumstances are met, including hydrodynamic shear stresses in the wall and vascular receptor expression. They must adhere firmly to the walls of the blood vessel, and then, depending on their ultimate objective, regulate cellular absorption, either avoiding or promoting it. This is what it's all about. The intravascular "journey" of the particle, which can be broken down into three events: marginalization dynamics, tight adherence, and regulated internalization, is explained in the description. The importance of particle geometry the role of (size and shape) is examined in each of these occurrences. Regardless of the plan taken, particles introduced into the vessel must avoid detection in order to be successful. The reticulo endothelial system (RES), a complicated network of phagocytic cells that line the liver sinusoids, removes debris from the bloodstream. This system collects in the red lymph nodes, bone marrow, and spleen pulp. It has been demonstrated that the size of the particle has a major influence on RES clearance: particles of 10 μm have been demonstrated to build up permanently, while those of μm and larger have been linked to liver and lung embolisms. in the spleen's open circulation. A common approach to extend the circulation half-life and avoid RES detection for sub micrometer particles is to decorate them. the particles that have polymer chains (PEG) [11].

❖ Shape

Spherical, rod-shaped, disc-shaped, and asymmetric shapes have different effects on endocytosis. Rod-shaped or disc-shaped particles sometimes have longer interactions with the membrane and can exhibit more efficient penetration. The energy required to deform the membrane is strongly dependent on the particle shape (Figure 1).

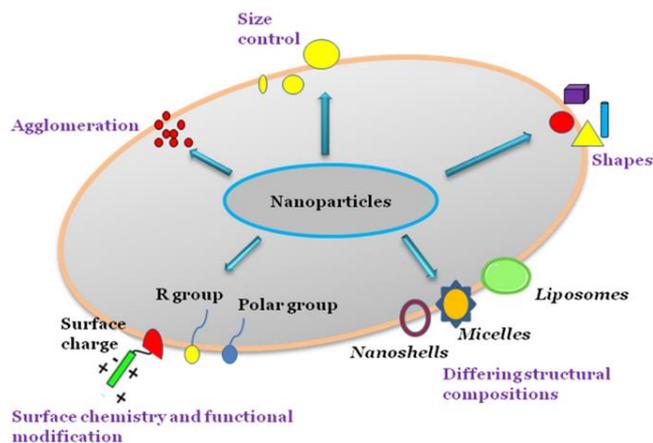


Figure 1: Various physical and chemical properties of nanoparticles (Yusuf et al., 2023).

❖ Surface charge

Positively charged nanoparticles tend to interact with negatively charged cell membranes and enter cells more easily. However, high positive charge can increase cytotoxicity and protein aggregation. Negatively or neutrally charged particles usually have longer circulation times but are less likely to enter cells.

❖ Stiffness or Flexibility

Soft or flexible nanoparticles are more easily deformed and cross membranes. Stiff particles may have lower entry but have higher structural stability. Dispersion and colloidal stability of particle aggregation can alter the entry pathway and reduce drug delivery efficiency. Appropriate stabilization (via surfactants or polymers) improves delivery efficiency [7].

❖ Advanced Mechanisms of Cellular Interaction and Uptake

Curvature, facilitate clathrin-mediated endocytosis by minimizing the membrane bending energy required for engulfment [7]. In contrast, the internalization of non-spherical geometries is more complex. High-aspect-ratio nanorods often require a sequential, energy-intensive "wrapping" process, while nanodisks necessitate a large, unfavorable membrane deformation, leading to significantly slower uptake kinetics [7]. Furthermore, shape can dictate the specific endocytic pathway; elongated particles often enter via caveolae-mediated endocytosis or macropinocytosis, which alters intracellular trafficking and drug fate compared to the clathrin pathway typically used by spheres [14].

Under fluid shear stress in vasculature, shape critically influences margination and adhesion. Rod-shaped particles exhibit a tumbling motion that increases their contact time with the endothelial lining, enhancing the probability of forming firm, multivalent bonds with surface receptors like ICAM-1. This makes them superior to spherical particles for targeted delivery to inflamed or tumorous eIn-Depth Comparative Analysis of Shapes for Specific Applicationsndothelium [2, 6].

❖ In-Depth Comparative Analysis of Shapes for Specific Applications

The optimal nanoparticle shape is highly context-dependent, varying with the biological barrier. While spheres are internalized most efficiently in 2D cell cultures, this does not translate to superior performance in vivo. For instance, in 3D tumor spheroids, elongated particles with intermediate aspect ratios demonstrate superior penetration, navigating the porous extracellular matrix more effectively than spheres, which are more prone to becoming trapped [14]. This highlights a critical paradox where the best shape for cellular uptake may not be the best for tissue penetration.

Beyond drug delivery, shape is a powerful tool in immuno-engineering. Anisotropic particles, such as ellipsoidal artificial antigen-presenting cells (aAPCs), present surface cues in a spatially controlled manner that leads to more effective T-cell

activation than spherical aAPCs, offering a novel platform for cancer immunotherapy [8]. Similarly, disk-shaped "cellular backpacks" can be designed to resist phagocytosis, allowing them to adhere to the surface of motile cells like T-cells and be physically hitchhiked into deep tumor tissues.

❖ The necessity of investigating the shape of nanoparticles as a key factor in drug delivery

Nowadays, in modern drug delivery, many efforts are being made to optimize the pharmacological action of drugs and reduce their side effects. Unfortunately, due to the low absorption of drugs in the body, the drug concentration in their blood plasma fluctuates due to their quick metabolism and rapid drug excretion. Furthermore, certain medications cannot be given intravenously because they are not very soluble in water. Finally, the vital access of drugs is still not completely clear; therefore, the medication concentration in the blood plasma fluctuates. In order to solve this problem, we must use drug carrier systems, which are efficient at releasing pharmacological and biological molecules to target areas in the body at a regulated and optimum rate; therefore, they not only increase the therapeutic effect of the drug, but also reduce undesirable side effects. One of the successful solutions in the field of controlled release (spatial and temporal) is the use of colloidal systems. Among colloidal carriers, liposomes and nanoparticles have been studied more than the rest. Liposomes are mainly made of cholesterol and lecithin; finally, it has good biocompatibility, but due to low stability (drug leakage) and low drug absorption efficiency, polymeric nanoparticles have replaced liposomes as a new drug carrier system [10]. The purpose of this study is to review the effect of nanoparticle shape on drug delivery and to present the best shape of nanoparticles for better drug delivery.

Materials and Methods

We reviewed research articles on how the form of nanoparticles affects the distribution of drugs, studied 20 research articles and selected the top 11 articles from them and conducted our studies with them. Our selection criteria focused primarily on clinical research examining the impact of nanoparticle form on medication delivery in a variety of illnesses, including cancer, drug delivery with nanoparticles, and the effect of nanoparticle shape on better penetration into cells. We conducted our studies from 2017 to 2025 and tried to present the best nanoparticle shape, which we presented in the results section.

Results and Discussion

Recent studies in biological systems have revealed that the physical characteristics of nanoparticles, such as their size, shape, and surface charge, may have an impact on how they are nonspecifically absorbed into cells. In addition, this results in a variety of consequences. The systemic distribution of nanoparticles and their interaction with cells are thought to be significantly influenced by particle shape. For example,

Because of their high surface area, numerous binding sites, and extended half-life in the bloodstream, worm-like magnetic nanoparticles are a better nanomaterial platform for targeting and imaging. tumors in vivo and aid in the more effective administration of medications to biological targets. However, there is still not much known about how particle shape affects its behavior. on cellular responses including cell division, apoptosis, adhesion, migration, and cytoskeleton development [3].

The three nanoparticles created by Huang et al. (2010) had different shapes and particle diameters, chemical compositions, and surface charges, but their aspect ratios were distinct (ARs, 1, 2, 4). All three nanoparticles were composed of monodispersed mesoporous silica (MSNs). They next studied the effects of particle shape of these three particles with different shapes on cellular uptake and behavior. The results showed that these particles with different shapes were easily absorbed into A375 human melanoma cells (A375) by non-specific cellular uptake. Particles with larger ARs were absorbed in larger amounts and had faster uptake rates. Similarly, particles with larger ARs were found to have greater effects on various aspects of cellular function, including cell proliferation, apoptosis, cytoskeleton formation, adhesion and migration [5].

Numerous studies have concentrated on creating agents to target the endothelium in sick tissues, such as the identification of antibodies against adhesion molecules and neovascular expression. peptides or markers identified via phage display. Furthermore, nanoparticles have been delivered to the endothelium of diseased tissue using such targeting compounds [1]. Researchers reported in 2013 that the specificity of endothelial targeting can be further enhanced by engineering the shape of ligand-displaying nanoparticles. According to microfluidic experiments resembling blood arteries (synthetic microvascular networks), rod-shaped nanoparticles have demonstrated greater specificity and less nonspecific buildup in the target flow as compared to spherical nanoparticles. Mathematical modeling of particle surface interactions indicates that the higher affinity and selectivity of nanorods results from a balance of multivalent interactions that cause adhesion and entropy loss, as well as shear-induced detachment that reduces binding [6].

Researchers looked at various nanoparticle forms in 2017, such as fluorescent mesoporous silica nanoparticles (MSNs), long rod nanoparticles (NLR), short rod nanoparticles (NSR), and spherical nanoparticles (NS). to systematically investigate their behavior in vivo after oral administration. An ex vivo optical imaging investigation in mice revealed the following findings. that rod nanoparticles persisted longer in the gastrointestinal system than spherical nanoparticles. The liver and kidneys were the primary sites of absorption for all oral MSNs, as demonstrated by in vivo biodistribution. NLR was able to effectively counteract rapid clearance. by RES and demonstrated a longer circulation period than NSR and NS.

Spherical nanoparticles were eliminated more quickly during renal excretion than rod nanoparticles. In addition, it was discovered that MSNs are capable of breaking down *in vivo*, with NSR breaking down more quickly than NLR and NS, most likely because of its larger specific surface area. The pharmacokinetic data revealed that nifedipine (NI) in NLR has greater bioavailability than in NSR and NS. [16].

Considering the shape of red blood cells with their oxygen-carrying and shape-facilitated diffusion capabilities, by coating disk-shaped mesoporous silica nanoparticles with red blood cell membranes, the scientists created synthetic red blood cell-like nanoparticles (RNDs). The results showed that compared with their spherical and rod-shaped isoforms with uniform drug release profiles, RNDs exhibited a drug-on-demand release pattern that mimicked natural red blood cells, i.e., they could rapidly release oxygen and loaded doxorubicin (DOX) under hypoxic conditions but were relatively stable in high-oxygen regions. Furthermore, the disk form also allowed RNDs to aid in transportation into the extracellular matrix of the tumor, which contributed to improving tumor permeability. RNDs, which are systemically delivered, effectively penetrate tumor tissue in tumor models, successfully alleviate tumor hypoxia, and alter the cancer cell cycle state from G₁ to G₂ phase, and increase the susceptibility of cancer cells to DOX, which is linked to greater chemotherapy effectiveness. Conversely, nanorods have reduced permeability and nanospheres. have inadequate medication buildup inside the tumor [12].

To bridge the gap between *in vivo* and *in vitro* studies and to examine how the form of nanoparticles affects cellular absorption and tumor penetration, the scientists created *in vitro* models of elongated polystyrene (PS) nanoparticles with the same chemical makeup and zeta potential but different aspect ratios (ARs). These nanoparticles' physical characteristics, cellular uptake, tumor penetration, and associated mechanisms were extensively studied. It was discovered that elongated PS particles with higher ARs demonstrated best ARs in a three-dimensional spheroid model evaluated, but had lower uptake rates in a two-dimensional cell monolayer culture model *in vitro*. Although elongated PS particles had similar tumor penetration mechanisms (mainly via extracellular pathways), the percentage of penetration using these mechanisms was strongly dependent on the ARs [14].

Emerging Frontiers and Future Perspectives

The next frontier lies in developing stimuli-responsive, shape-transforming nanoparticles that dynamically adapt to their environment. For example, particles can be engineered to circulate as long-circulating filaments or rods and morph into spheres upon encountering the acidic tumor microenvironment (pH-triggered) or specific enzymes like MMP-2/9 (enzyme-triggered), thereby switching their function from vascular margination to efficient cellular internalization [9, 15].

Computational design and AI are becoming indispensable for navigating the vast design space. Multiscale modeling predicts interactions of various shapes with biological barriers, while machine learning algorithms analyze high-throughput data to identify optimal design parameters, moving the field from empirical testing to rational design [4]. Furthermore, research is exploring fractal and other bio-inspired shapes that offer unprecedented surface-to-volume ratios or unique propulsion capabilities, mimicking efficient biological structures found in nature.

Conclusion

Endocytosis is known to be influenced by the physical properties of micro- and nanoparticles, such as their size, charge, and shape. The drug uptake efficiency and subsequent effectiveness of the medication may be enhanced by improving the drug carriers' physical design. The endocytotic capacity of basic forms, like the sphere and cylinder, has been examined. Various particle shapes were made using keyboard characters to study the shape effect on cellular uptake, and their effects on cellular absorption were evaluated. According to the data, forms with larger aspect ratios and more acute angular characteristics are more likely to bind to the cells and be absorbed by the cancer cells. The local interaction between the cell membrane and the part of the microparticle in contact with the cell membrane also plays a crucial role in determining the outcome.

The size, shape, surface characteristics, and material makeup of polymer-coated nanoparticles (NPs) are four crucial factors in creating effective nanoparticle-based carriers for targeted drug administration. However, most research produces ambiguous descriptions of the shape relationship because of the intricate interaction between size, form, and surface characteristics. Large-scale molecular simulations have been carried out to investigate convex nanoparticles with varying forms in order to better understand how PEGylated nanoparticles affect cellular absorption. by comparing systems with the same nanoparticle surface area, ligand-receptor interaction strength, and polyethylene glycol bond density in the shapes of spheres, rods, cubes, and discs, we discover that those spherical nanoparticles have the fastest internalization rate, followed by cubic, rod-shaped, and disk-shaped nanoparticles. As a result, among these nanoparticles with varying shapes, spherical nanoparticles exhibit the greatest absorption. A thorough free energy analysis reveals that the shape the primary way that nanoparticles cause an effect is through the different membrane bending energies that occur throughout endocytosis. Compared to non-spherical nanoparticles, spherical nanoparticles must overcome a minimal membrane bending energy barrier, while the internalization of disk-like nanoparticles requires significant membrane distortion, which causes a high free energy barrier, whereas the bending energy barrier is relatively small. Additionally, we discovered that, much like their spherical counterparts, star-shaped nanoparticles are quickly enveloped by the cell membrane, indicating that they may be Utilized to deliver drugs with great efficacy. Our results appear to provide useful guidance in the molecular design of PEGylated

nanoparticles for regulated cellular uptake and aid in the establishment of quantitative principles in the development of nanoparticle-based carriers for targeted drug delivery.

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Declarations:

Authors' Contribution:

- ^cConceptualization,
- ^aData collection, drafting of the manuscript
- ^{b-d-e} Intellectual revisions
- The authors agree to take responsibility for every facet of the work, making sure that any concerns about its integrity or veracity are thoroughly examined and addressed

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