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Advances in particle shape engineering for improved drug delivery

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Spherical particles such as liposomes and microspheres are the most common and extensively applied drug vehicles. However, researchers have come to realize the superiority of nonspherical nanoparticles. Actually, in human bodies red blood cells, gut biotics and many well-known pathogens have distinct shapes. It can be reasonably inferred that particle shape plays a pivotal part in human bodies. In this review, we summarize the recent studies about the effect of shape on delivery processes such as cellular uptake, tissue penetration and biodistribution. The underlying mechanisms that are relevant to the phenomena revealed, owing to experimental and computational modern techniques, will be addressed, and we shall provide future perspectives on particle design to improve the efficacy of drug delivery.

Introduction

Nanotechnology has advanced the development of pharmaceutics during the past decades, and particulate-based drug delivery systems have shown great potential to improve the bioavailability and efficacy as well as reduce adverse side effects [1]. In addition to material engineering and surface modifications, the bioinspired design of nanoparticles (NPs) has received much attention [2,3]. In particular, particle shape, one of the fundamental properties of NPs, has been suggested to facilitate many aspects of the drug delivery process. Additionally, some phenomena in human bodies that can be considered the result of natural selection and evolution imply the importance of the effect of shape. For instance, most microbiomes in the intestinal mucus appear to be nonspherical [4]. Pathogens with a strong invasion ability could take advantage of their unique shape. With increasing evidence available, researchers have realized the distinctive advantages of shape engineering when designing drug carriers.

By contrast, various biological barriers in human bodies severely limit the application of NPs. Cellular uptake and intracellular trafficking remain the major obstacles to drug delivery and therapeutic effects [5,6]. Tissues such as mucosa and tumors contain complex structures with considerable depth that severely impede the penetration of drug-loaded NPs, reducing the absorption or targeting efficacy [7,8]. The reticuloendothelial system (RES) can destroy and clear the foreign NPs during circulation [9]. These issues indicate the urgent need to further redesign and improve the properties of NPs. Tuning the particle shape, a general physical characteristic, can be safe and cost-effective [10]. In this review, we first provide a brief introduction about engineered NPs with different morphologies; then, we summarize the research advances of particle shape that affect *in vivo* behavior during the delivery process, such as cellular uptake, tissue penetration, blood circulation and organ distribution. Emphasis will be placed on deep insight into the underlying mechanisms of shape phenomena, together with the admirable contributions by computational simulation works. Perspectives about the future design of NPs based on the choice of shape will be addressed.

Engineered particle shape

Successful fabrication of NPs with desired properties is a fundamental procedure. Recently, materials science has developed impressive approaches to fabricate NPs with various shapes, although the field is far from achieving freely controllable synthesis of scalable particles. In particular, a majority of shape-effect studies are based on inorganic NPs and studies on biodegradable, usually organic, NPs are rare to the best of our knowledge.

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TABLE 1

Recent advances in shape effect on biobehaviors during different delivery processes

Advantageous process	Particle shape	Materials	Comments	Refs
Cell-related issues	Rod and disc	Polyethylene glycol diacrylate-based hydrogel	Discs can internalize more effectively, and larger rods and discs have higher uptake than smaller ones	[20]
	Sphere, rod and disc	Polystyrene	The order of uptake efficiency is rod > disc > sphere	[23]
	Sphere and rod	Mesoporous silica; gold	Rods with AR of 2 are taken up in larger quantities than NPs with other ARs	[22,26]
	Sphere and rod	Mesoporous silica	Longer rods (AR = 4) have a faster internalization rate and higher uptake rate than spheres and shorter rods	[25]
	Sphere and sheet	Amphiphilic PAMAM-b-OEG co-dendrimer	The main uptake mechanisms for spheres are macropincytosis-dependent and clathrin-mediated endocytosis, and for nanosheets it is clathrin-mediated endocytosis; nanosheets exhibit higher antitumor activity	[29]
	Sphere, rod and worm	Poly(oligoethylene glycol methacrylate)-block-poly(styrene-co-vinylbenzaldehyde) block copolymer	Together with computational modeling, experiments revealed no significant differences in the escape time from early or late endosomes; however, rods and worms entered the nuclei more effectively by passive diffusion	[32]
	Sphere and rod	Mesoporous silica	Rods have a higher enrichment in and detection efficacy of circulating tumor cells	[33]
	Rod, cubic and octahedral	Cerium oxide	Rods significantly and dose-dependently enhanced the cytotoxicity response	[34]
Tissue penetration	Sphere, rod and disc	Polyethylene-glycol-based nanohydrogel	Discs with very low AR emerge to be ideal for maximizing the accumulation in tumors; increasing the AR of rods cannot improve the penetration	[36]
	Sphere and rod	Polystyrene	Nanorods can display longer intestinal retention and are transported by the lymph to a higher extent	[41]
	Sphere and rod	Mesoporous silica	Experimental and theoretical works support the superior diffusion of rods over spheres based on the mechanism of rotation pattern and hopping effect; the diffusivity can be much higher with rods having an optimized AR	[39,40]
Long circulation & biodistribution	Sphere and rod	Poly(DL-lactide)-b-poly-(acrylic acid)	Different endocytic pathways lead to the higher uptake of spheres by macrophages	[44]
	Rod with high AR	Plant virus	Higher blood vessel margination results in the enhanced delivery to thrombolytic sites	[47]
	Rod with different AR	Mesoporous silica	Short rods are more likely to accumulate in the liver, whereas long rods are readily trapped in the spleen	[9]
	Rod and star	Gold	Protein adsorption can be affected by the size, shape and probably surface area	[48]
	Sphere and rod	polystyrene-b-poly (ethylene oxide) micelles	Elongated micelles have delayed clearance by the liver; the rigid core causes short circulation of elongated micelles	[49]
	Sphere, rod and worm	Glycidyl methacrylate- oligo(ethylene glycol) methyl ether methacrylate copolymer	*In vivo* biodistribution showed that small spherical particles have higher tumor accumulation and low healthy tissue distribution	[50]
Other utilities	Sphere, rod and disc	Polystyrene	Rods provide the highest uptake efficiency and improved specificity for breast cancer cells	[51]
	Cage and solid sphere	Iron oxide	Cage-shaped NPs have a desirable release profile in the tumor microenvironment and provide improved efficacy	[52]
	Star	Low molecular weight (MW) PCL polyols crosslinked with isocyanate	Retention in the stomach associated with ultra-long-acting drug delivery	[53]

For inorganic NPs, particle shape can be driven by altering the kinetics of surface facet growth during the wet-chemical synthesis to form various morphologies, such as rods, stars and wires [3,11] (Fig. 1). Template-driven methods have been widely applied in the fabrication of inorganic NPs such as mesoporous silica nanoparticles (MSNs). A typical template method consisted of three steps: template preparation, particle formation and template removal [3]. Anisotropic multidimensional and multicompartmental particles with intriguing morphologies are subject to extensive research [12]. The morphology of graphene can also be precisely and facilely controlled, and hybrid materials containing graphene with distinct shapes have been shown to improve cancer therapy [13,14]. New efforts will be devoted toward exploring simple, easy to scale-up, cost-effective and ecofriendly approaches.

Organic NPs, by contrast, are considered more likely to be biodegradable and have been investigated in the majority of studies, and most organic NPs are polymer-based particles. Scalable manufacturing of differently shaped polymers is challenging but is becoming more and more achievable. Great efforts have been devoted to the shape engineering of polymeric particles during past decades. Polystyrene particles with incredibly diverse shapes could be generated through the reformation in a film made

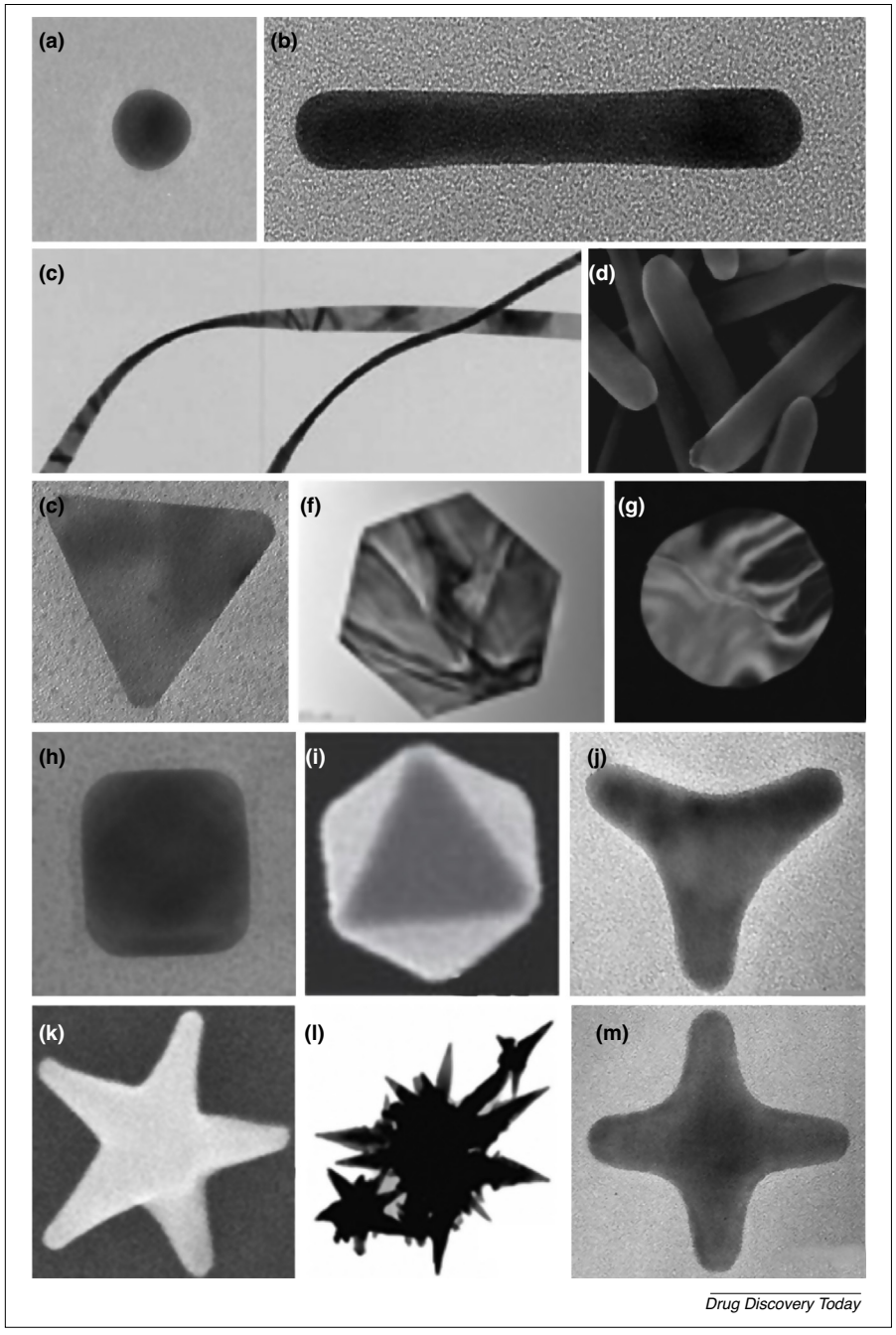

FIGURE 1

Metallic nanoparticles (NPs) with distinct shapes. The particle shapes are (a) sphere, (b) rod, (c) belt, (d) wire, (e) triangle, (f) hexagon, (g) disc, (h) cube, (i) octahedron, (j) tripod, (k) star, (l) thorn and (m) tetrapod. Reprinted, with permission, from Ref. [3].

of, for example, poly(vinyl alcohol) (PVA) [15]. Although the biodegradability of polystyrene NPs might not be ideal, such a method could be a useful tool. DeSimone and co-workers [16] have reported a method (particle replication in non-wetting templates; PRINT) to fabricate cylindrical poly(lactic acid-co-glycolic acid) (PLGA) NPs with high loading efficacy. This approach suggests a promising future for obtaining organic NPs with highly controllable shapes. Agarwal *et al.* [17] improved the scalability and ease of imprint-surface modification by designing a biopolymer-based sacrificial layer, the solubility of which was switchable, to achieve shape-specific fabrication of NPs. Liposome-based rod-shaped NPs have also been developed for vaginal vaccine delivery [18]. It could be expected that, because of the urgent need, an increasing number of state-of-the-art strategies will emerge to facilitate shape engineering. With the appearance of versatile, simple, economic and scalable methods, NPs made from different materials with novel morphologies will be created to benefit a variety of *in vivo* particle functions and achieve precisely controlled behaviors during drug delivery. Nevertheless, careful attention should be paid to the possibility that polymeric or lipid-based NPs can swell, partially degrade and deform, making it more challenging to reveal the actual shape effect [19].

Shape effect on different delivery processes

Successful drug delivery requires tackling one of or, more often, a combination of challenging issues, such as cellular uptake, intracellular transport, tissue penetration, biodistribution and prolonged circulation. Great efforts have been devoted to address these issues, and particle shape engineering has emerged as a generally feasible approach. These issues will be discussed in detail in the following sections from a cell-based microscopic view to a systematic perspective. A brief summary has been presented in Table 1.

Cellular uptake and intracellular transport

The shape effect on cellular uptake and transport-related issues has been the most widely investigated effect but it remains controversial. Researchers have devoted great efforts toward revealing how the particle shape influences the binding process, uptake efficiency and intracellular transport. Rod- and disc-like nonspherical NPs are most commonly used for comparisons with spherical ones [20,21]. An early report compared the cellular uptake efficiency of MSNs with different aspect ratios (ARs, ratio of length and width) and demonstrated the overall superiority of rods (AR > 1) over spheres (AR = 1) [22]. Meanwhile, disc-shaped polymeric particles were shown to internalize even more effectively than their rod counterparts [20]. A recent study, however, found that the order of uptake efficiency was rod > disc > sphere [23]. Controversial issues existed in other respects as well – together with the shape effect, increasing the size of different-shaped NPs can further improve [20,24] or impede [23] the internalization rate. Even the optimal AR of rod-shaped NPs, which can be most effectively internalized by cells, remains a controversial issue [25–27]. Some results supported long rods (AR = 4), whereas others backed up short rods (AR = 2) which possessed a faster internalization rate and higher uptake amounts. Despite the contradictions, the local curvature turns out to be the fundamental factor determining the initial membrane-wrapping rate [28]. If all the other conditions are the same, a particle with sharp morphology will be internalized by a cell more effectively. However, it should be noted that uptake is an energy-requiring process, so the materials and particle volume must be taken into consideration [20,24]. Also, it has been revealed that the main uptake mechanisms for sheets and spheres are different, which consequently influences tumor accumulation [29]. Therefore, an optimized uptake efficiency could be achieved through the rational choice of shape, size and materials with respect to certain target cells. Interestingly, reports have even taken the targeting ligand into consideration and illustrated that ligands modified on the body-side of rod-shaped NPs would have more opportunities to interact with cell membranes or receptors and therefore achieve a higher cellular uptake [23,26,30].

The intracellular fate of NPs is seriously associated with the issues of lysosomal escape and subcellular targeting. It has been demonstrated that rod-shaped NPs with high ARs or sharp curvatures could rapidly destroy the lysosomal membrane [28]. Nevertheless, there are controversial results indicating that the intracellular fate would not be altered by the shape of NPs [31,32]. Hinde *et al.* [32] recently assessed the escape transit time of spheres, rods and worms from early and late endosomes, but no significant differences could be detected. Interestingly, however, they found that rod- and worm-shaped NPs could more rapidly enter the nucleus by passive diffusion and therefore achieved a higher delivery rate for nuclear-targeting drugs such as doxorubicin. Apparently, deliberate particle morphology engineering can improve the subcellular targeting efficacy.

The shape effect could have clinical significance with respect to not only drug delivery but also diagnosis. Recently, Chang *et al.* [33] compared the ability of rod- and sphere-shaped MSNs to detect circulating tumor cells in cancer patient blood samples, revealing that rods had faster enrichment and higher sensitivity than spheres (Fig. 2a). Above all, however, the issue of safety should be taken into consideration. Forest *et al.* [34] pointed out the higher potential of nanorods to induce proinflammatory and cytotoxicity responses. Shape engineering for improved effects should never exclude the principle of safer-by-design.

Tissue-penetrating ability

Most NP-based drug delivery studies are aimed at delivering therapeutics into the deep tumor. However, the tumor contains a dense stroma, the extracellular matrix which is a tight network, preventing the NPs from effective permeation and restricting them at near-vascularized regions of tumors [8]. Particle size has been widely studied to boost particle retention in the tumor, whereas not much attention has been focused on the correlation between particle shape and tumor penetration until recently [35]. However, many factors can affect *in vivo* consequences; for instance, vessel margination ability and circulation clearance, which will be detailed in a later section. Hence, it is difficult to draw fair, rigorous conclusions asserting which shape can diffuse rapidly in the tumor matrix. Recently, Agarwal *et al.* [36] adopted 3D spheroids as an *in vitro* tumor tissue model and detected maximal accumulation of disc-shaped hydrophilic NPs with a very low AR. They also pointed out that increasing the AR of rods would not affect their penetration into spheroids, and another report indicated the adverse effect of higher AR on tumor permeation [37]. Although there

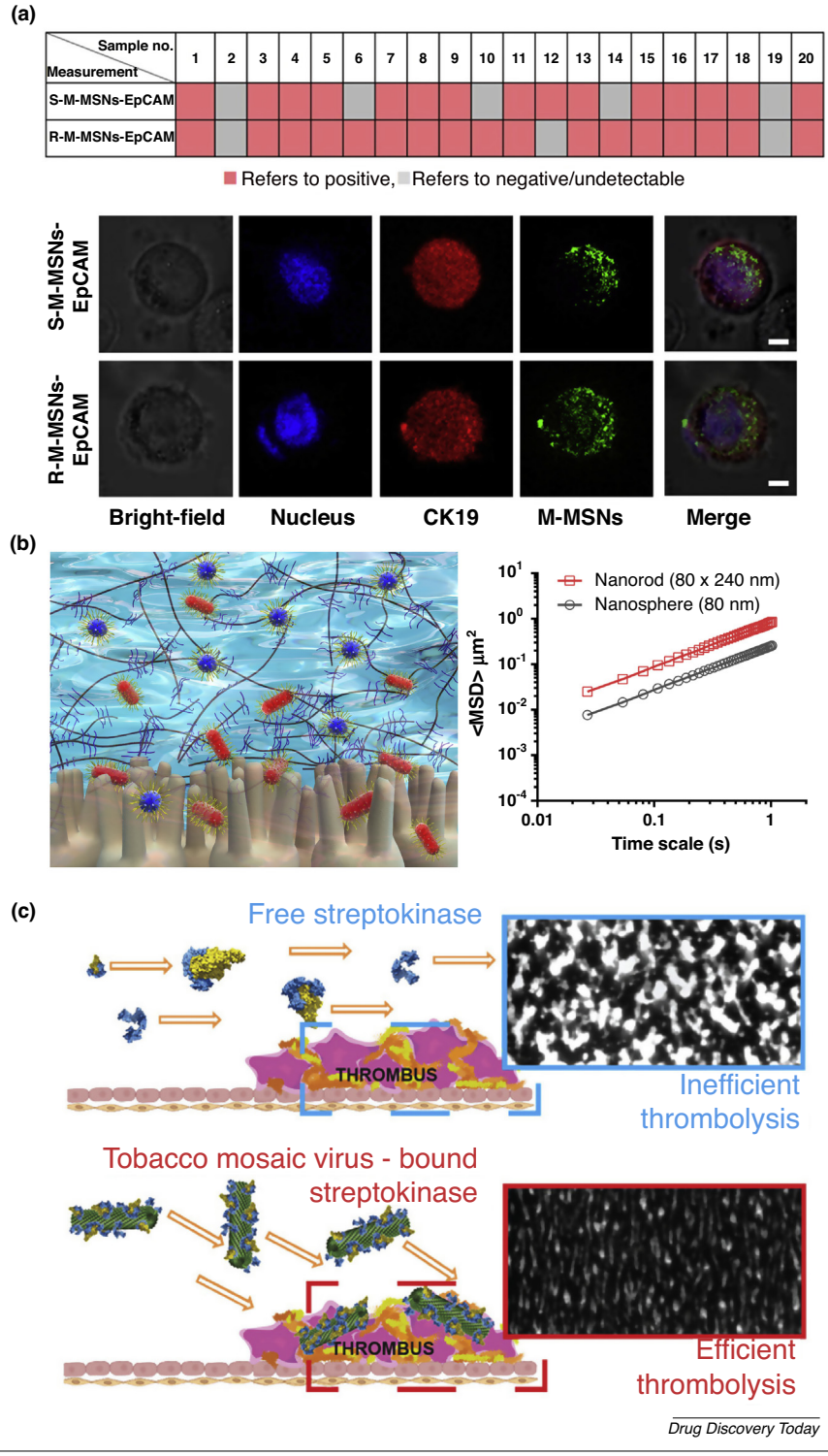

FIGURE 2

Effect of particle shape on different biobehaviors. (a) Effect on cellular uptake: rod-like magnetic mesoporous silica nanoparticles (MSNs) conjugated with antibodies against epithelial cell adhesion molecule (EpCAM) could more effectively detect circulating tumor cells in clinical blood samples from breast cancer patients. (b) Effect on tissue penetration: rod-shaped MSNs could diffuse faster than spherical MSNs in the intestinal mucus. (c) Effect on vessel margination: elongated plant-virus-based vehicles exhibited margination effect during circulation and were more promising for the treatment of thrombosis. Reprinted, with permission, from Refs [33,39,47].

are many different tumor types, the tumor extracellular matrix can share some similarities with respect to physical mechanics. Shape engineering might turn out to be a widely accepted strategy to improve the penetration of NPs.

Another extensively investigated tissue is the mucosa, which is highly related to the drug absorption and is exposed in a variety of organs, such as the gastrointestinal tract, lung and nose. It is composed of a mucus layer of a certain thickness at different sites

and the underlying epithelia, protecting the human body from pathogens and toxins. The intestinal mucus, for instance, is a viscoelastic gel mainly composed of water and mucin, which form into a gel-like structure with pore sizes ranging between 100 nm and 800 nm that mechanically hamper the transport of NPs [6]. Conventionally, mucolytic agents could be used to break the mesh structure, but this might risk exposing the body to pathogens. PEGylation is another classic approach, but densely PEGylated NPs are not easily taken up by cells [38]. Recently, we have demonstrated that mesoporous silica nanorods could diffuse much faster than their spherical counterparts in the intestinal mucus [39] (Fig. 2b). Additionally, there exists an optimal AR of rods to reach a maximal diffusion in mucus [40]. Similar gastrointestinal retention effects of rods have been demonstrated as well and the rods can be more easily transported into lymph, achieving lymphatic delivery through oral administration [41]. Without further biochemical modification, shape engineering can serve as an ideal approach to facilitate rapid transport in these gel-like tissues.

Biobehaviors in circulation and organ distribution

In addition to cell- and tissue-based internalization and trafficking issues, a prolonged circulation time and desirable biodistribution will improve the general efficacy. Quick degradation or removal of NPs will limit the therapeutic efficacy, whereas unexpected tissue accumulation will lead to severe side effects. In contrast to the preferred cellular uptake mentioned in the previous section, macrophage uptake during circulation usually results in the clearance of circulating NPs, which could account for the unexpectedly short duration of NPs [42,43]. Uptake of rod-shaped NPs with a high AR by macrophages has been found to be lower than their spherical counterparts [44]. Moreover, on the basis of hydromechanics, the rod-like shape-mediated margination effect can benefit the adhesion and accumulation of NPs, avoiding rapid clearance [45], and therefore allowing long duration of rods. Geng *et al*. [46] fabricated wormlike micelles and achieved a 1-week circulation time, which was approximately ten-times longer than that of spheres. *Pitek et al*. [47] took advantage of this margination effect and designed elongated plant-virus-based NPs, achieving localized delivery for the treatment of thrombolytic disease (Fig. 2c). The protein corona is another crucial factor during circulation, which can remarkably affect the behaviors of NPs. It has been demonstrated that particle shape can also influence the composition of the adsorbed protein [48]. More efforts should be devoted in the future to systematically understand the shape effect in protein corona and the consequent biobehaviors.

By contrast, organs have distinct preferences for differently shaped NPs. Avoiding the unexpected aggregation of NPs in certain organs can effectively reduce the potential toxic events in tissue. Huang *et al*. [9] have demonstrated that short-rod MSNs were more quickly cleared than long-rod MSNs. After careful tissue imaging and examination of the final fate of particles, they found that short rods were mostly trapped in the liver, whereas long rods were trapped in the spleen. Similarly, Jennings *et al*. [49] compared the biodistribution of spherical and rod-like micelles at different time points and showed that elongated micelles had remarkably delayed liver clearance. Short circulation, however, was found for elongated micelles with a rigid core. Recently, Kaga *et al*. [50] investigated polymeric NPs with various shapes and found that polymeric spheres were more likely to accumulate in tumors whereas filamentous ones tend to be distributed in healthy tissues. These results suggest comprehensive control of various characteristics of NPs, instead of the shape alone, can be crucial.

Other utilities of shape effect

In addition to the abovementioned diverse advantages, shape engineering can bring other revolutionary functions as well. Antibody-conjugated rod-shaped NPs could not only provide higher internalization but also improve the specificity compared with that of their spherical and disc counterparts [51]. Such specificity generated by the particle shape could receive further investigations to pave the way for the rational selection of particle morphology. In terms of drug release, Rampersaud *et al*. [52] explored the release profile of cage-shaped NPs and showed that particle shape could even affect the release rate in the tumor microenvironment. Moreover, Langer and co-workers [53] meticulously designed a star-shaped formulation to realize the retention of the vehicle in the gastric mucosa for ultra-long-acting drug delivery. With a better understanding of the biological systems, more functions provided by the shape effect will be discovered.

Computational-simulation-aided mechanism studies

For the purpose of rational design, studies on shape effects should not be limited to the phenomenon but should place more emphasis on elucidating the underlying mechanisms. The combination of theoretical predictions and experimental observations will provide a deeper insight into the mechanisms, followed by the generation of theoretical models guiding the future design of drug delivery vehicles. Owing to the rapid development of advanced equipment and computational technologies, a variety of theories established recently have provided useful guidelines for shape engineering of particles with different requirements. Coarse-grained molecular dynamics (CGMD) simulation is a popular approach to investigate biological transitions. Shi *et al*. [54] applied this method combined with experiments to demonstrate that rod-shaped 1D particles enter cells by the tip first, and they suggested that tip-specific modification could avoid cytotoxic frustrated uptake. Recalling our discussions in the previous sections, the optimal shape and AR for cellular uptake remain controversial. In terms of simulation works, some have even indicated that spherical NPs are more easily internalized by cells [55], whereas others supported the superiority of NPs with an optimal AR [56] (Fig. 3a,b). The rotation and switch of NPs has been suggested as an important mechanism that causes shape-dependent endocytic efficiency [56–58]. Despite those disputes, Yang and Ma [59] adopted dissipative particle dynamics, a common CGMD simulation, to reveal that factors including shape effect (local curvature of the particle at the contact point), particle volume and initial orientation cooperate together to influence the interactions between the particle and cell membrane. Bias can exist in experimental comparisons, because particle volume, fluorescence intensity per particle and number of particles are not identical, which will remarkably affect the results. With the help of computational simulations, the parameters of particles are con-

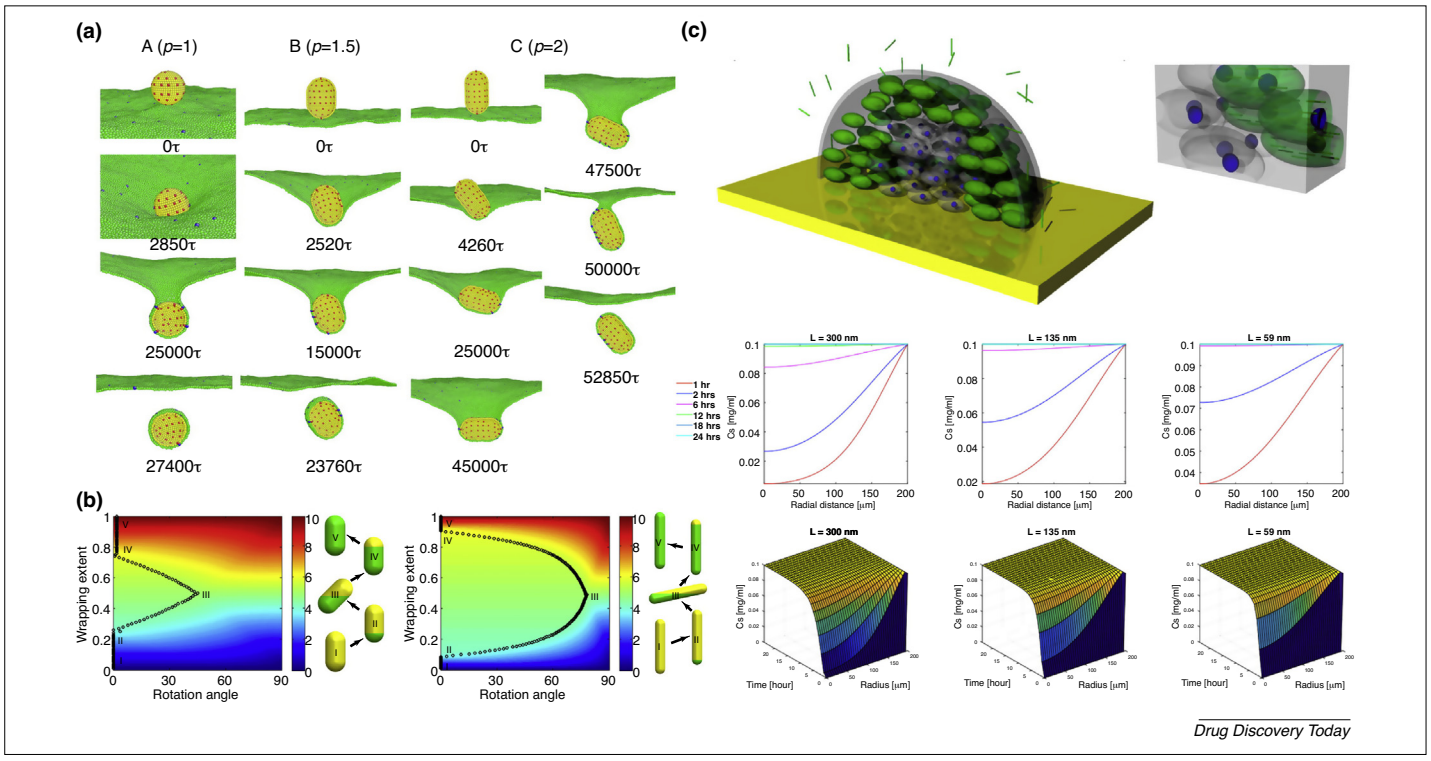

FIGURE 3

Theoretical model-aided illustrations of shape effect. (a) Nanoparticles (NPs) with a medium aspect ratio (AR) have the highest internalization rate. (b) The higher the AR of NPs, the larger the rotation angle that rods adopt to minimize the wrapping energy. (c) Effect of particle AR on spheroid penetration. As the AR decreases, NPs penetrate the tissue at an increasing rate. Reprinted, with permission, from Refs [37,56].

trollable and can be easily adjusted to be identical; and, therefore, we can have a clear, reliable understanding of the shape effect.

Other shape effects investigated through computational modeling approaches have also received substantial attention. Chariou *et al.* [37] developed a mathematical model and predicted the superior distribution of short-rod-shaped viruses diffusing in a spheroid system compared with the spheres and longer rods (Fig. 3c). Tan *et al.* [45] investigated the distribution of NPs with different shapes in a mimetic branched blood vessel and showed that, under shear flows, most rod-shaped NPs would bind to the vessel wall, whereas spheres were more likely to be quickly removed. The results also indicated that rod-shaped NPs would be more useful when targeting the organs with complex branched vessels. Similar margination advantages have been confirmed for oblate particles with moderate ARs as well [60]. In our previous work, we not only captured the rotation and hopping diffusion of rods in mucus via stimulated emission of depletion (STED) microscopy but also applied CGMD simulations to propose models addressing the mechanism of the superior mucus-penetrating ability of rods [39,40]. The theoretical work was even extended by addressing distinct diffusion patterns of nanorods with different ARs in adhesive (i.e., mucus) and non-adhesive polymeric gels. These fundamental theories proposed made the experimental findings more convincing and could definitely guide the future design of drug delivery systems. Nevertheless, modeling usually simplifies the complex situations in nature, and therefore should never be treated independently. Experiments are indispensable for verifying the predictions by computer simulations.

Concluding remarks and future prospects

In addition to particle size, zeta potential and materials, shape has been shown to be a crucial factor that remarkably influences the *in vivo* fate of NPs during drug delivery. The various superior features of nonspherical NPs have been explored from a microscopic perspective, such as improved cellular uptake and considerable tissue penetration, to a systemic view, such as prolonged circulation time and favorable biodistribution. Owing to the advanced technologies and deeper understanding of biological systems, increasingly optimized particle shapes will be created to improve the particle delivery efficacy. Meanwhile, contradictions regarding the optimal shape and aspect ratio imply that factors including shape, size, materials and even target cells usually interact and should be considered comprehensively. Computational modeling offers well-controllable characteristics of NPs for the convenience of achieving deeper insight into those complex biological events and providing guidance for the future design of NPs. Nevertheless, experiments are always essential to verify the theoretical models, validate the safety of novel vehicles and avoid possible bias. Despite the sophisticated environment encountered by the NPs, a simple design is desired for the ease and feasibility of scalable manufacturing. It should be noticed that most current studies focused on inorganic materials, but biodegradable materials with distinctive morphology might receive more attention. It can be expected that rational shape engineering of drug delivery systems will benefit the biomedical field in the future.

Conflicts of interest

The authors have no conflicts of interest to declare.

Acknowledgments

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