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Non-Spherical Particles for Targeted Drug Delivery

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Abstract

Nano- and microparticles loaded with various bioimaging contrast agents or therapeutic molecules have been increasingly used for the diagnosis and treatment of diseases and tissue defects. These particles, often a filled or hollow sphere, can extend the lifetime of encapsulated biomedical modalities in circulation and in target tissue. However, there is a great need to improve the drug loading and targeting efficiency of these particles. Recently, several simulation and *in vitro* experimental studies reported that particle shape plays a pivotal role in the targeted delivery of molecules. To better understand these findings and subsequently expedite the use of particles in biomedical applications, this review paper summarizes the methods to prepare non-spherical nano- and micro-scaled particles. In addition, this review covers studies reporting the effects of particle shape on the loading, delivery and release of encapsulated bioactive cargos. Finally, it discusses future directions to further improve the properties of non-spherical particles.

1. INTRODUCTION

In the past several decades, polymeric nano- and microparticles have been used in various industrial and household products, because their unique physiochemical properties and structure can significantly improve product quality and performance. For instance, particle-based systems can elaborately control rheological properties of paints and coating materials, optical properties of cosmetics, and mechanical properties of concrete [(1)]. Recently, efforts were made to harness the advantages of micro- and nanoparticles in fundamental and applied bioscience studies, including diagnosis, bioimaging, and therapeutics.

In biomedical applications, nano- and microparticles can prolong the half-life of therapeutic drugs and bioimaging contrast agents, and subsequently enhance binding or uptake by target host cells [(2)]. For example, biomolecules loaded into polymeric carriers retain their

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bioactivities longer than free biomolecules directly administered into circulation [3,4]. Nanoparticles with diameters ranging from 10 to 100 nm are known to passively accumulate in the extravascular space of tumor, due to the enhanced permeability and retention (EPR) effect [5]. Additionally, surface modification of nano- and microparticles with peptides, antibodies, or other ligands to receptors, can help induce active targeting, thus elevating the targeting efficiency of particles in conjunction with the EPR effect. Despite the improvements offered by nanoparticles in biomedial applications, improving nanoparticle drug encapsulation, half-life, and targeting remains a grand challenge.

Recently, there is growing evidence that particle shape may influence particle targeting, drug release, and imaging contrast efficacy. According to several fundamental studies, particle shape significantly affects transport properties of particles in fluids, and further affects adhesion kinetics of the particles to target cells [6,7]. As such, efforts are increasingly made to tailor particle shape at different length scales, which are used to enhance biomedical applications. To assist this effort and further enhance the targeting efficiency of particles, this review article systematically reviews the different methods to control particle shapes, and further investigates the effects of particle shape on diagnostic and therapeutic efficacy of particles.

2. METHODS TO CONTROL PARTICLE SHAPES

Various methods devised to control particle shapes can be divided into two major ways – chemical modification of particle-forming polymer or modification of a pre-existing spherical particle into a non-spherical shape. The latter approach is advantageous for preparing particles with narrow size distribution; however, due to technical limitation, the minimum controllable size of particles is approximately a few hundreds of nanometers.

Chemical modification of particle-forming polymer

Amphiphilic block copolymer and hydrophobically modified graft polymer have been increasingly used to produce nanoparticles with a range of unique shapes. For example, flower-shaped aggregates with about a few hundred micrometers in diameter could be formed by cross-linking the hydrophobic domain of poly(ethylene oxide)-b-poly(N-acryloxysuccinimide) (PEO-b-PNAS) di-block copolymer on silicon wafers (Fig. 1a). The PEO-b-PNAS formed spherical micelles in the absence of cross-links on a glass slide [8]. A tri-block copolymer, folate-poly(ethylene glycol)-poly($_{D,L}$-lactide)-poly(ethylene glycol)-acrylate (FA-PEG_{114}-PLA_{293}-PEG_{46}-acrylate) also led to nano-sized, worm-like vesicles, where PEG_{114} constitutes the outer layer (Fig. 1b). The PEG_{46}-acrylate that formed an inner layer of the worm-like micelle could be cross-linked to enhance stability *in vivo* [9]. In addition, the self-assembled ellipsoidal polymersome were formed by chemically coupling a proper number of PEG chains to poly(2-hydroxyethyl aspartamide)-g-octadecyl chains (PHEA-g-C_{18}) (Fig. 1c). In contrast, the PHEA-g-C_{18} free of PEG tethers formed a spherical vesicle [10].

It is also possible to control particle shape by modifying the particle processing technique, while keeping the pre-existing chemical structure the same. Worm-like micelles of poly(ethylene oxide)-b-poly(-caprolactone) (PEO-PCL) with a few micrometers long could

be prepared by removing the sonication step during a solvent exchange process. Here, the mass fraction of the hydrophilic PEO was around 0.5, allowing for the formation of an elongated micelle. In contrast, the sonication dispersed the elongated micelles into spherical particles [(11)]. The non-spherical PEO-PCL micelle completely transformed to a spherical one within 200 hours due to hydrolytic degradation of at the PCL end units [(12)]. Based on end-cleavage mechanism, the hydrophilic component of PCL was hydrolytically cleaved over time, thus prompting the transformation of the shape [(12)].

Modification of particle assembly process

Non-spherical polymeric particles could be also fabricated using various assembly devices including microfluidic devices [(13,14,15)], particle replication in non-wetting template (PRINT) [(16)], and film stretching [(6,17)].

(1) Microfluidic device—This unit allowed production of particles with uniformly desired shapes on a micrometer length scale. By applying UV-light through a pre-defined mask, the resulting unit created PEG diacrylate (PEGDA) particles with various shapes, because particles could be only formed under the transparent part of the mask. These shapes include flat polygonal structures, high-aspect-ratio rods, and curved particles with a size range of 10 to 50 μm; however, the shape feature could be only modified in 2D with controlled thickness (Fig. 2a) [(13,14)]. Separately, photo cross-linkable tripropyleneglycol diacrylate (TPGDA) was used to prepare non-spherical particles, without using a pre-defined mask. By irradiating the pre-gelled polymer solution with a controlled droplet volume through a narrow microfluidic channel, microparticles with shapes of rod, disk, and ellipsoid could be readily prepared (Fig. 2b) [(15)].

(2) Particle replication in non-wetting template (PRINT) [(16)]—Using a mold with an array of negative microwells of controlled shapes, this PRINT unit enabled massive production of particles with pre-defined shapes [(16)]. To date, poly(methyl methacrylate) (PMMA) was used to generate conical- and trapezoidal-shaped particles.

(3) Film stretching—Instead of obtaining non-spherical particles directly through a microfluidic process or PRINT, non-spherical particles could be prepared by stretching spherical particles embedded in a poly(vinyl alcohol) (PVA) film [(17)]. For instance, pre-made spherical poly(styrene) (PS) microparticles were stretched into an ellipsoidal shape with a draw ratio from 1.5 to 2.6 by controlling the degree of stretching [(17)]. This technique also allowed preparation of particles with various non-spherical shapes by controlling heat and choosing a proper solvent. This process created oblate ellipsoidal, prolate ellipsoidal, and UFO-shaped particles [(6)].

(4) Packing—Small non-spherical clusters were generated by packing spherical particles through chemical bonding or trapping holes (Fig. 2c) [(18,19)]. Depending on the number of spherical PS particles, tetrahedron, triangular dipyramid, and more geometric shape were found in clusters [(18)]. Moreover, single-layered and double-layered clusters were prepared by tuning the diameter and thickness of trapping holes in which PS particles were inserted [(19)].

(5) Others—Instead of the methods mentioned previously, there are some other, more unusual ways to assemble non-spherical particles. For instance, by reducing the concentration of PS latex concentration below ~20% in oil, disk and toroid-shaped microparticles were created [(20)]. In a separate process, hollow PS particles with shapes similar to red blood cells (RBCs) were also generated by inducing collapse of spherical hollow PS particle through either solvent or heat-induced fluidization [(21)].

3. EFFECTS OF PARTICLE SHAPE ON BIOLOGICAL FUCTION

Loading efficiency, targeting efficiency and release rate of drug molecules are key factors in designing drug carriers. There is growing discussion and evidence that particle shapes significantly influence these characteristics, according to both in vitro and in vivo studies.

Drug loading efficiency

Worm-like micelles present larger core volume than spherical ones, thus allowing loading of more hydrophobic drug molecules via double emulsification [(12)]. For instance, the hydrophobic tubular center of a PEO-PCL worm-like micelle loaded two-fold higher paclitaxel (TAX), an anticancer agent, compared to spherical core [(11)]. A similar finding may be also achieved with vesicles used to encapsulate hydrophilic drugs, because ellipsoidal vesicles would have a larger internal volume than spherical ones.

Drug release rate

The release rate of drug molecules, specifically macromolecular drugs with a size larger than the pore diameter of the nanocarriers, is significantly influenced by the degradation of particles. A faster degradation of drug carriers typically leads to a higher drug release rate. For example, a cross-linked worm-like vesicle has a slower drug release rate than a non-cross-linked one [(9)]. To date, there is no clear evidence showing that shape affects particle degradation. It was suggested that non-spherical particles have a release profile distinct from spherical ones because the inhomogeneous thickness over the non-spherical particle may lead to different local degradation rate and unique release profile [(22)]. However, the measurement of release rate of TAX-loaded micelles from one study did not display a significant difference in drug release profile between spherical and non-spherical particles during incubation at different conditions or after several freeze-thawing cycles at −20 °C [(11)].

Targeting efficiency

Nano- and microparticles carrying drug molecules were often functionalized with bioactive peptides or antibodies that can adhere to target cells or tissue, in order to deliver drugs of interest to target pathologic tissue. Additionally, nanoparticle size was tailored to promote transport into extravascular space around leaky inflammatory or tumorigenic vasculature via EPR mechanism. Throughout these efforts, it is now well agreed that two major factors affect quality of targeted delivery: (1) transport property and (2) binding efficiency of drug carriers in circulation. Recent studies have increasingly reported that particle shape modulates both factors.

The particle shape affects transport properties of particles in circulation, such as flux, volumetric flow rate, and retention time. Computational studies demonstrated that non-spherical particles under blood flow-like stream presented different force and torque profile over the surface compared to nanospheres. Therefore, at a certain flow rate, the spherical particles remained in circulation, while elongated ones moved towards vascular walls. Subsequently, elongated particles would have a higher accumulation level on target pathologic vascular wall than spherical ones leading to enhanced therapeutic efficacy in local injection [23,24].

Similarly, the computational analysis of rod-shaped nanoparticle and spherical nanoparticle with the same volume showed that the adhesion efficiency of nanorods to target vasculature was higher than that of nanospheres [25,26]. In vitro particle adhesion study conducted with a blood vessel-mimicking flow chamber also confirmed that more nano-sized rods or ellipsoids were attached to endothelial cell monolayer than nanospheres [10,25].

Efforts were also made to assemble PS particles with shapes similar to RBCs in order to harness unique transport properties of RBCs. It is well known that RBCs are flexible enough to deform their bodies and pass through capillaries with a smaller cross-sectional diameter. Although there is no explicit evidence that RBC-mimicking particles have enhanced adhesion efficiency to target tissue, improved circulation performance still offers the potential for particles to deliver drug molecules. A controlled release study of Texas Red-conjugated dextran demonstrated the capability of RBC-mimicking particles to release macromolecules over 10 days [21].

Separately, it is common to control the targeting efficiency of particles by chemically or physically conjugating ligands to a particle surface at a given density. Interestingly, recent simulation studies reported that a rod-shaped particle presented at least 2-fold higher binding affinity to a spherical one with the equivalent internal volume (the same drug loading capacity) when they were subject to different shear rates [25]. The underlying mechanism was attributed to a larger surface area of elongated particles than spherical ones, and, subsequently, about 20 % more targeting ligands on the surface for nanorods with an average aspect ratio of 3 [25,27]. In accordance with the simulation study, an *in vitro* study with endothelial cells also showed that elongated nanoparticles with an aspect ratio of 2.1 displayed approximately 2-fold higher adhesion efficiency compared to spherical ones [10]; moreover, *in vivo* distribution study with mice displayed that accumulation of nanorods coated with anti-intracellular adhesion molecule antibody (anti-ICAM-mAb) in lung and liver was about 2-fold of nanospheres [27].

Additionally, the particle shape significantly influenced cellular uptake efficiency, most notably in the 20 nm size range. For instance, cells took up nanoparticles with rod, worm, and ellipsoidal shapes more efficiently than spherical ones, likely because of the difference of curvature between particles. Therefore, elongated particles were advantageous for intracellular drug delivery.

More interestingly, certain studies have demonstrated that different particle shapes have led to varied cell uptake levels. Xia et al. recently reported that gold nanorods and nanocages

could penetrate into the core of solid tumors, whereas gold nanospheres and nanodiscs only localized on the tumor surface [28].

In addition, macrophage particle uptake is highly dependent of particle shape and size reported by Mitragotri et al. For example, macrophages endocytose rod-shaped particles, stretched from 0.5 μm spherical particles to about 5 μm in length, more actively than oblate ellipsoids and spherical particles [29]. This finding reflects the mechanism by which macrophage ingest bacteria of varied shapes at different rates.

4. CONCLUSION AND FUTURE DIRECTION

In summary, non-spherical nano- and microparticles with various shapes including ellipsoid, rod, and worm could be prepared by chemically modifying particle-forming molecules, devising a specific particle assembly, and applying external mechanical forces to particles. These non-spherical particles were advantageous to improve drug delivery efficiency compared with spherical ones, because of increased drug loading efficiency, enhanced attachment to a vascular wall (a larger binding affinity to target cells and tissues), and also better cellular uptake efficiency. Overall, non-spherical particles present a great potential to overcome barriers that current drug delivery strategies are encountering with use of spherical drug carriers, although more thorough *in vivo* studies should follow. In addition, there are still a few challenges to be resolved for assembly and performance of non-spherical particles: (1) broad size distribution of non-spherical nanoparticles formed from self-assembly and (2) limited controllability for sustained drug release. Fundamental studies on chemistry and physics underlying particle assembly would take the controllability of morphology, properties, and functions of non-spherical particles to the next level. Subsequently, these efforts will greatly expedite the use of drug carriers in clinical treatments of various diseases and tissue defects.

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- Non-spherical particle can be used in different medical applications.
- Non-spherical particle have longer in vivo half-lives than spherical particles.
- Elongated particle can be easily taken up by cells due to unique curvature profile.
- Non-spherical particle enhance the targeting efficiency by more bound ligands.

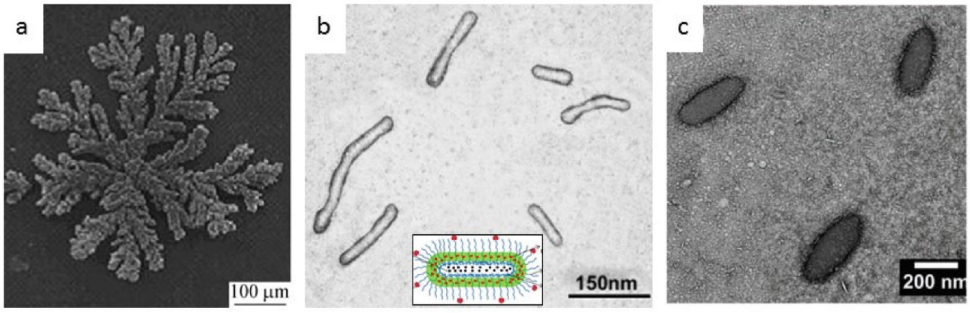

Figure 1.

Self-assembled non-spherical particles: (a) flower-shaped aggregate [8], (b) worm-like vesicles [9], and (c) ellipsoidal polymersomes [10].

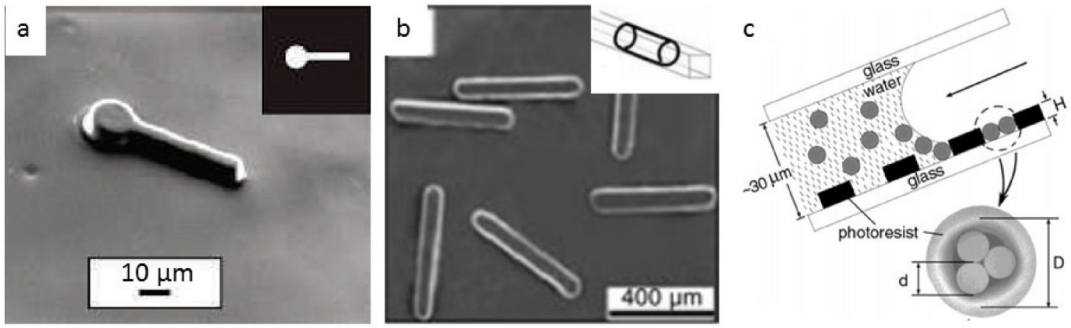

Figure 2.

Non-spherical particles through modified fabrication processes: (a) high-aspect-ratio PEGDA particle [(14)], (b) rod-shaped TPGDA particles [(15)], and (c) non-spherical cluster with controlled numbers of PS particles prepared through trapping holes [(19)].