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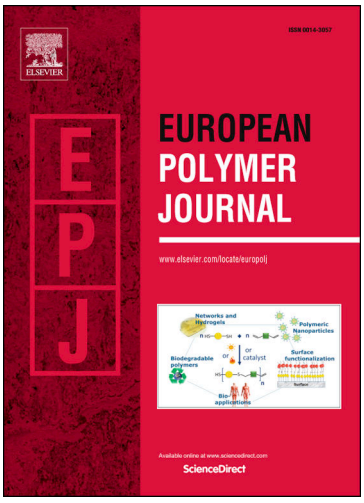

Role of particle shape on efficient and organ-based drug delivery

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Role of particle shape on efficient and organ-based drug delivery

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Abstract

Encapsulation of drugs in nano- and microparticles has been known as a promising approach for efficient drug delivery. It has been well established that adjusting the physiochemical properties of these carriers concerning the specific condition of each disease will improve therapeutic efficacy. The role of particle characteristics including composition, size, surface chemistry, density, elasticity on successful drug delivery has been well recognized. In the last few decades, particle shape arose as an important property playing a profound role in drug delivery efficiency. Particle shape plays its role by affecting physiological interactions including opsonization, internalization, margination, circulation half-life, etc. Delivery of a drug carrier to its target site is a desirable goal in drug delivery, and we were wondering whether engineering the particle geometry would bring us closer to this goal. This article has aimed to review researches studying the impact of particle shape on its interactions with the physiological environment and to focus on the role of particle shape in targeted drug delivery to various sites including liver, spleen, lung, brain, and also tumor sites of different tissues.

Keywords: drug delivery; nonspherical particles; particle shape; targeted drug delivery; delivery systems

1 Introduction

In biomedical applications, nano- and microparticles have been proved to be useful for the early detection, bioimaging, vaccination, and therapy of various diseases [1]. They can prolong the half-life of therapeutic drugs and bioimaging contrast agents and enhance uptake by target host cells [2]. Drug delivery vehicles like liposomes, polymeric micro and nanoparticles, micelles, carbon nanotubes, microbubbles, virus-like particles, dendrimers, and quantum dots have been introduced so far [3]–[7]. These particles have several advantages, such as the possibility of tailoring their properties to improve the efficiency of available therapies, protecting the drug from degradation, providing a controlled and prolonged drug release, and offering active or passive targeting to the tumor site [8]. It should be considered that after the administration of particles, they face a complex environment that exposes them to plentiful interactions, including interactions with serum proteins, different cell types, fluid dynamics, and various biological barriers. All above-mentioned interactions can lead to some challenges such as difficulties in crossing biological barriers, rapid particle elimination from the blood circulation by the reticuloendothelial system (RES), early release of the drug, and aggregation after interaction with serum components, quick removal from the bloodstream, and a low target efficiency [9].

These challenges converge researchers' concentration on evaluating the effects of particle characteristics on drug delivery efficiency [10]. The role of particle size is well described previously and has a large impact on particle fate in vivo. The size of carrier profoundly affects its behavior in the biological environment. For example, nanoparticles with diameters < 5nm are eliminated from blood circulation through extravasation or renal clearance rapidly, however particles with diameters up to the micrometer range accumulate in liver and spleen. Besides, surface modification plays an important role in tailoring surface of particles to allow a better adaptation to the physiological surroundings, for instance, PEGylation increases hydrophilicity, improves stability, prevents opsonization and prolongs in vivo circulation time [11].

Recently, particle shape attracts increasing attention as a new parameter that can affect particle fate in vivo. Spherical particles have been used extensively as drug carriers because of their simple fabrication methods [12]. With the advancement of particle fabrication technology, nonspherical carriers like ellipsoidal (oblate and prolate) [13], [14],discoidal [15], [16], cylindrical [17], worm shaped, rod shaped [18], tubes [19]–[21], wires [22] and cubic particles [23]–[25] have emerged recently. This article discusses common methods for the preparation of nonspherical

particles and then reviews the role of particle shape in particle internalization to the cells, -circulation time, margination, biodistribution, cytotoxicity, and drug release profile.

2 Micro- and nanoparticle fabrication methods

There is a wide array of techniques that are applied in the fabrication of spherical drug carries. Methods that can be used in the preparation of particles depend on particles' components and also desired characteristics of particles. Today, polymeric carriers are virtually the most prevalent systems that are used in drug delivery. Fabrication methods of these carriers are classified based on whether they are being fabricated from monomers or from preformed polymers. The former class contains several methods, including emulsification polymerization and dispersion polymerization. The latter class involves different methods, such as solvent evaporation and solvent extraction processes, phase separation, evaporative precipitation, antisolvent precipitation, spray drying, electrospraying, and microfluidic [26].

2-1 Nonspherical particles fabrication methods

Various methods are now available for the fabrication of nonspherical particles. Here we will summarize some of them, which have been widely used in drug delivery applications.

2-1-1 Self-Assembling Methods

Self-assembling of surfactants and amphiphilic block copolymers are widely used for fabrication of particles with the capability of tailoring particle properties including size, stability, and release properties [27]. The size and shape of particles in this method depend on the chemical composition of the reaction components and the ratio of hydrophilic and hydrophobic segments, in addition to the conditions of the self-assembly system. Particles with various shapes such as vesicles, cylinders, and lamellae have so far been obtained using this technique [28], [29]. A schematic illustration of the self-assembling method is given in figure (1).

Although this method is cost-effective and energy-efficient, the final shape is limited to some thermodynamically stable geometries such as vesicles, lamellae or cylinders and cannot be precisely controlled [29].

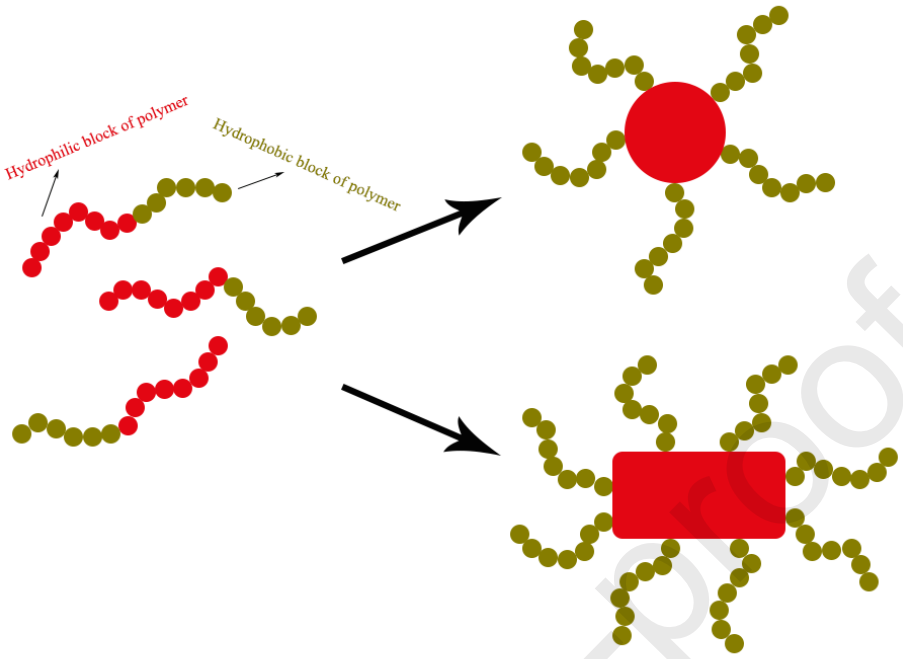

Figure 1 Schematic illustration of self-assembling method: Hydrophilic and hydrophobic blocks of polymer are self-assembled to form nonspherical particles.

2-1-2 Microfluidics

Microfluidic devices allow the fabrication of uniform particles with desirable size and shape [30]. Figure (2) shows a schematic illustration of microfluidics. The starting materials of this technique can be divided into two phases, including continuous phase and dispersed phase, which can be a low melting-point lipid or a UV-curable polymer. This method consists of following steps: pinching off the droplets of the dispersed phase into the continuous phase, solidifying droplets either by in situ polymerization or lyophilization, and obtaining solid particles [31]. Nano- and microparticles of various materials have so far been fabricated using this technique. Microfluidic systems provide the possibility of preparing particles with desirable size, shape, and porosities through adjusting the flow rates of continuous and dispersed phases, polymer concentration, molecular weight, and chemical nature of the polymers. In addition, particle shape can also be controlled by applying proper microchannel geometry. Different particle shapes, such as spheres, plugs, and discs, have been obtained using this method [29].

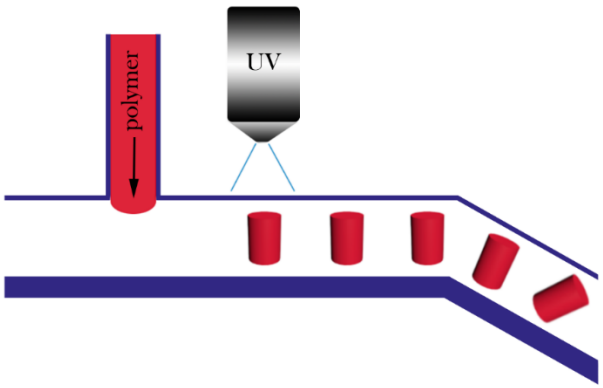

Figure 2 Schematic illustration of the preparation of nonspherical particles using a microfluidic system. The outlet channel defines particle shape.

2-1-3 Particle replication in non-wetting templates

Particle replication in non-wetting templates (PRINT) technique consists of following steps: preparing a silicon template by applying techniques which are commonly used in the microelectronic industry, preparing an elastomeric mold often using perfluoropolyether (PFPE) which is demonstrated to be non-wetting to organic and inorganic compounds, filling the mold with precursor solution, solidifying the precursor in the mold via solvent evaporation or photocuring, removing solid particles from the mold cavities using an adhesive film and dispersing particles in a solution by dissolving the film [32], [33]. Figure (3) indicates a schematic process of the PRINT method. Nano- and microparticles with various geometries such as cube, rod, cylindrical, hexnuts, and donut have been generated using this process. This technique has been applied for different materials such as proteins, lipids, and other biocompatible and biodegradable polymers. The PRINT technology gives the possibility to precisely control size, shape, flexibility, surface properties, however, this method is a multi-step process, and mass production of particles still is elaborating [34].

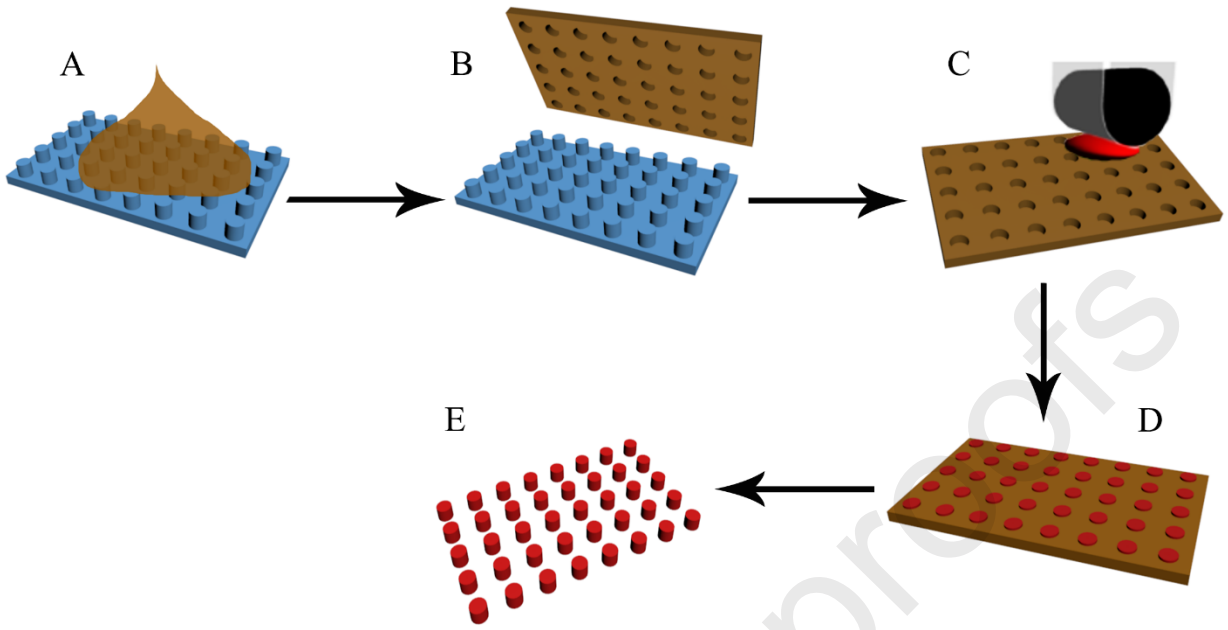

Figure 3 Schematic illustration of PRINT method process: (A) a liquid polymer mold (brown) is delivered onto a silicon master with desired shape and size (blue); (B) polymer is peeled away to generate a mold with cavities; (C) roller is brought into contact with particle solution and the mold; (D) particles are cured in the mold; (E) nonspherical particles with desired shape and size are harvested.

2-1-4 Film stretching

Unlike previous methods, this method uses spherical particles as starting materials. Film stretching technique consists of the following steps: embedding spherical particles in a film or a gel, liquefying particles using heat or a solvent that is a nonsolvent for the film or gel, stretching the film or gel that leads to deformation of particles, solidifying deformed particles by cooling or solvent extraction, dissolving the film or gel, washing and purifying of recovered particles [34], [35]. The process of this method is illustrated in figure (4).

A variety of shapes with different aspect ratios can be obtained using this technique, including spheres, rods, worms, circular discs, rectangular discs, and elliptical discs. The ultimate particle shape is controllable through various parameters including temperature, stretching rate, stretching dimension, and film/gel properties. For instance, using high temperatures or more plasticizer will cause low particle viscosity, which subsequently leads to flat shapes. Mass production in this method is problematic because films should be stretched individually; hence particles cannot be produced continuously [29].

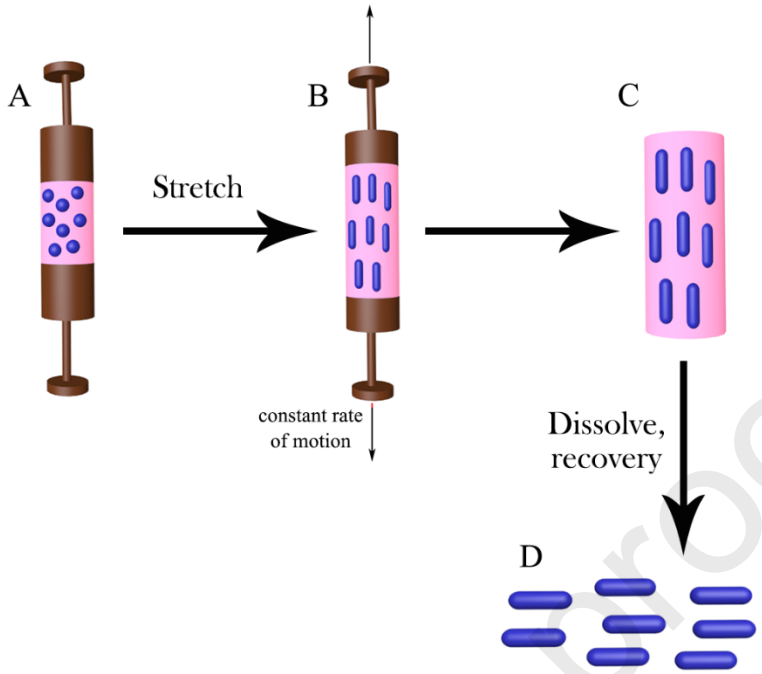

Figure 4 Schematic illustration of film stretching method process: (A) liquefaction of spherical particles by using heat or a solvent; (B) stretching the film in one or two dimensions; (C) eliminating the motion; (D) dissolving the film forming material and harvesting the nonspherical particles.

2-1-5 Other methods

There are also many other approaches that can be used for the preparation of nonspherical particles using various materials. Jet spinning, electrospinning, step and flash imprint lithography, continuous flow lithography, hydrogel template method, and packing are some other approaches that have been used in order to prepare nonspherical particles [36], [37].

3 Role of particle shape on drug delivery efficiency

3-1 Internalization

A particle must evade macrophages uptake, particularly in the reticuloendothelial system, to travel successfully and reach to its target. On the other hand, the particles should be designed in a way that internalize to normal or cancerous cells and release the therapeutic agents inside the cells. Cellular uptake and uptake mechanism depend on particle shape in addition to particle size and surface chemistry. Shape effect on

particle internalization is very important because of the importance of endocytosis and prevention of phagocytosis [38].
The effects of particle shape on internalization have been related to a contact angle parameter, Ω, which is a measure of local curvature that indicates both the curvature of the particle and the attachment point of a macrophage [39]. Particles with Ω<45 induce phagocytosis; in this range, phagocytosis velocity decreases with increasing Ω. Phagocytosis initiates by the formation of actin cup and completes by the closure of the membrane with suitable particle size and Ω<45. However, when Ω>45, the macrophages spread on the particle, and internalization does not occur [40].
Champion et al. displayed that IgG-coated 1-μm and 3-μm spherical particles showed about ten times higher internalization by rat macrophages in comparison to worm-like particles of those sizes. The internalization of a particle with a high aspect ratio (AR) is less probable than a particle with a low aspect ratio because only two points of attachment (the tips) have Ω<45 [39]. Figure (5-A) shows the internalization of a particle with a low aspect ratio that is more probable in comparison to a particle with a high aspect ratio (figure 5-B, C).

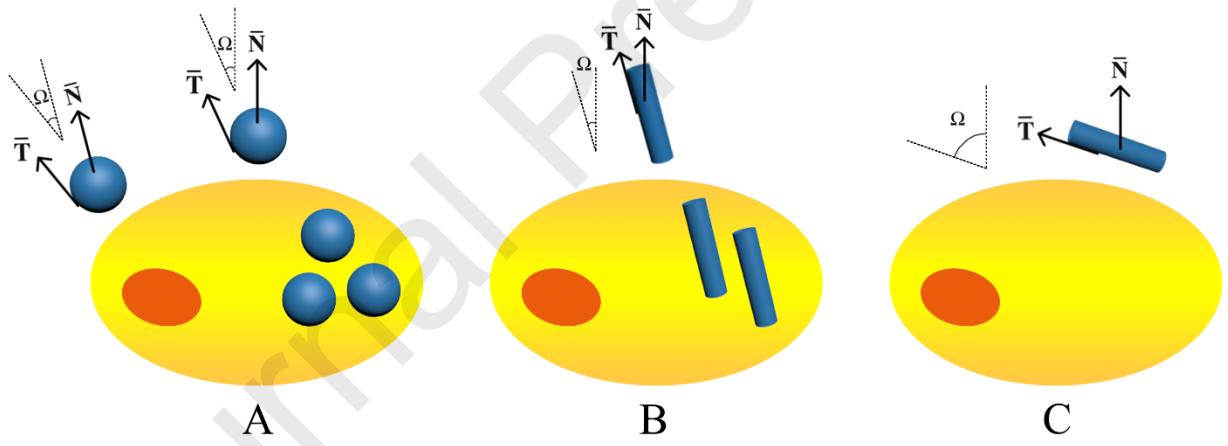

Figure 5 Effect of contact angle on the rate of particle internalization to cells: T represents the average of tangential angles near the point of cell contact. Ω is the angle between T and the membrane normal at the site of attachment, N̄. (A and B) Ω<45° and the rate of internalization is high; (C) Ω>45° and the rate of internalization is low.

It should be considered that phagocytosis is a combination of two phenomena, first the attachment of particle to the macrophage surface and second the internalization of the attached particle to the macrophage with a defined velocity [39]. An

experiment indicated that particle attachment for prolate ellipsoids (major axis: 0.35–2 μm; minor axis: 0.2–2 μm) is more than spheres (radius: 0.26–1.8 μm) and oblate ellipsoids (major axis: 0.35–2.5 μm; minor axis: 0.2–2 μm), while the highest rate of phagocytosis belongs to oblate ellipsoids because internalization rate is slow for prolate ellipsoids and spheres [41].

Agarwal et al. compared the cellular uptake of hydrogel nanodiscs and nanorods in several cell types, and the result showed that nanorods displayed a decreased cellular uptake [42]. An experiment indicated that filamentous block copolymer micelles have less internalization to the cells versus the spherical ones because they are extended by the flow under fluid flow condition [43].

Disc-shaped mesoporous silica nanoparticles had higher cellular uptake than spherical nanoparticles due to their porous system, resulting in a desirable application for the delivery of anticancer drugs [44]. Moreover, doxorubicin-loaded mesoporous silica nanorods showed higher cellular uptake and oral bioavailability in comparison to spherical particles [45].

Some researchers have proved that the difference of internalization between spherical and elongated shapes is more evident in primitive times, and after 3-5 hours will be decreased [41], [46], [47].

In some cases, the purpose is delivering the therapeutic agents into the cells, and endocytosis by the target cells is desired. Qiu et al. studied gold nanorods of different aspect ratios, and it was revealed that with increasing aspect ratio, the internalization of particles in human breast adenocarcinoma cell line decreases [48]. Zhang et al. compared the internalization of cylindrical and spherical nanoparticles in Chinese hamster ovary (CHO) cells; they showed that spherical shapes have a higher rate of entry into CHO cells than cylindrical nanoparticles. However, they indicate that functionalization of particles with a special protein increases cell internalization of spherical nanoparticles while it has no effect on cylinders [49].

Another important parameter for studying the effect of particle shape on cellular uptake is the type of cell; for example, epithelial cells internalize hydrogel nanodiscs more than nanorods under in vitro conditions [42]. Morover, the internalization of hydrophobic discoidal and rod-shaped nanoparticles was similar, but the story for hydrophilic hydrogels was different, and the nanodiscs were more efficiently internalized in comparison to nanorods [50].

It must be considered that particle size and surface charge are also effective factors on cellular uptake and uptake mechanism. Chunabi et al. indicated that macrophage uptake increases with increasing the particle surface charge (either positive or negative), most probably due to increasing electrostatic interactions between particles and phagocytic cells. Internalization into non-phagocytic cells increases with increasing positively charged of a particle surface because of more affinity to

the negatively charged of the cell membrane, although this behavior is cell line dependent either [51]
This research also compared the different sizes of particles in the range of 150-500 nm. Larger particles induced more phagocytosis by macrophages, and smaller particles had more internalization to the non-phagocytic cells because the larger particles need stronger driving force and additional energy for the cellular internalization process [51]

3-2 Circulation

Circulation time of drug delivery systems plays an important role in therapeutic efficacy, meaning that drug delivery carriers, which remain in the circulatory system for a short period, mostly possess low efficiency [28]. Achieving prolonged circulation is limited by different biological mechanisms, such as renal and RES clearance. Once a particle enters the circulatory system, it absorbs plasma proteins called opsonins, and then it will be taken up by macrophages in the RES. In order to improve drug delivery efficiency, drug delivery carriers should be able to evade clearance systems and remain in blood circulation for an extended period of time. This goal can be achieved by adjusting particle properties. Particle shape is considered as a crucial determinant in particle circulatory behavior by giving particles the ability to escape from the body's clearance mechanisms [52], [53]. Numerous studies have attempted to clarify the role of particle shape in circulation time. In some cases, theoretical studies using different computational models and in vitro findings using in vitro flow chamber systems provide different results with those of in vivo studies. This is thought to be due to in vivo conditions that are difficult to be simulated, such as adhesion to the vascular endothelia, uptake by cells of the RES and passing natural barriers in the liver, lung, and spleen [54]. In an experiment, it was shown that highly flexible filomicelles remained in circulation for around one week because they aligned with bloodstream and avoided vascular collisions, filtration, and phagocytosis. Arnida et al. compared blood levels of PEGylated gold nanospheres and nanorods after intravenous administration in mice. NRs had a plasma concentration of 11% of the injected dose, whereas spheres concentrations remained below 1% [55]. An experiment investigated the persistent circulation of spherical and filamentous micelles formed using diblock copolymers of PEG and the inert poly (ethylethylene) or biodegradable poly (ε-caprolactone). In this study filomicelles displayed longer circulation blood time. Moreover, it was shown that longer filomicelles up to the length of about 8 μm that is nearly the same with the diameter of red blood cells have longer circulation time [56]. In a study, blood circulation time of spherical and disc-shaped polystyrene particles was investigated and it was found that discs remained in the circulation significantly

longer than spheres, despite having nearly the same dimension. It is thought due to alignment of discs with blood flow, similar to discoid erythrocytes [57].
Other particle properties also have a great impact on in vivo circulation half-life of particles, including particle size, stiffness, and surface chemistry. By engineering these properties, prolonged circulation time will be achieved. Many researchers have investigated the effect of particle size on its circulation time. Their results have shown that spherical particles with diameters less than about 10 nm possess short circulation time because they are easily cleared from the body through renal clearance. On the other hand, among particles that are large enough to avoid renal clearance, larger particles also displayed shorter circulation time than smaller ones because they removed more rapidly due to higher opsonization and subsequent RES clearance. Surface modification is one of the most, if not the most, common strategies for prolonging circulation time. The goal of surface modification is preventing the absorption of plasma proteins, followed by preventing recognition by macrophages and deletion via phagocytosis. Experimental studies have demonstrated that surface charge is an important parameter affecting the clearance rate of particles. Particles with the positive surface are often cleared from the body rapidly because of increased opsonization. However, anionic and neutral particles have shown to remain in the circulatory system for longer times, due to reduced interactions with the RES. Numerous studies demonstrated that particles with lower stiffness display longer circulation time compared to those with higher stiffness, probably because higher stiffness induces more phagocytosis by macrophages [52], [53].

3-3 Margination

Successful delivery of micro- and nanoparticles to specific targeted sites consists of several steps; evading the numerous clearance mechanisms of the body, following the right direction in the circulatory system toward target tissue, escaping the blood flow and marginating towards the blood vessel walls and targeting the endothelium either actively via surface-bound ligands or passively via the enhanced permeability and retention (EPR) effect in leaky vasculature. Therefore, particles should be designed to move toward the endothelial walls, as white blood cells and platelets do during an inflammatory process. The margination of leukocytes and platelets is mediated by red blood cells that migrate to the core of the vessel due to hydrodynamic interactions with the walls (called lift force), leading to pushing particles toward the vessel wall [9]. It can be concluded that resembling particle shapes to those of red blood cells may prolong circulation time, and on the other hand, resembling their shapes to leukocytes and platelets may enhance margination propensity [58].

Margination propensity is mostly affected by diffusion and momentum forces and depends on a number of parameters that may be related to blood flow properties, vessel size, or particle features. Particle shape has been identified as one of the most effective parameters on the margination behavior of particles. Recently, many research groups have tried to investigate the effect of shape on margination, and their mathematical modeling and experimental studies have shown the crucial role of shape in margination. It has been shown that discoidal, rod shape, hemisphere, and ellipsoidal particles have higher margination tendency compared to spherical particles because spherical particles display minimal lateral drift and are less likely to marginate to vessel walls [59]. For example, in one study, nanorods displayed 7 times higher margination and deposition than nanospheres with nearly the same size under the same shear rate, probably due to variable drag forces and torques that they experienced underflow [60]. It has been shown that the aspect ratio is a determinant parameter that strongly affects lateral drift velocities of nonspherical particles. Drift velocity increases with increasing aspect ratio [61].

In addition to particle shape, there are several other parameters that have a considerable effect on particle margination, including flow rate, red blood cell deformability, hematocrit, vessel diameter, particle size and deformability that will be explained briefly.

Experimental studies have shown that smaller particles will lead to greater margination efficiency because for margination and deposition of a particle, diffusion of the particle must overcome its momentum. Since the diffusion coefficient decreases with the increasing size of the particle, the smaller particles will marginate easier due to their higher diffusion component [62]. ased on the Stokes-Einstein equation, particles with the same size should have the same diffusion coefficient. However, the momentum of particles of the same size depends on the particle's density and flow rate because the momentum is the product of mass and velocity. Hence, particles with higher density marginate with more difficulty than those with the same size but lower density due to their higher momentum [56]. The impact of flow rate on margination has been investigated, and the results have shown that margination inversely correlated with flow rate due to the increasing momentum component. In other words, the faster the blood flows, the more difficultly particles can evade from streamlines. For instance, it was shown that the deposition of 65 nm liposomes was about three times lower when the flow rate was four times faster. It has been found that margination and deposition propensity of particles depends on the vessel features such as vessel diameter and its geometry. Particles have shown more margination in small vessels compared to large ones, and also they have displayed more deposition propensity at bifurcations than along straight vessels [63]. Hematocrit is the ratio of the volume of red blood cells to the total volume of blood. It has been shown that margination increases when hematocrit

increases because the red blood cells tend to stay at the center of the blood vessel, so they force particles to move toward vessel walls like what happens to WBCs [64]. In another study carried out by cooley et al., polystyrene particles of four different shapes, including spherical, oblate, prolate, and rods from nano- to micro-scale sizes were fabricated using the stretching technique. Then, the interplay between particle size and shape with respects to margination and retention was perused through both computational and experimental approaches. It has been observed that micro-scale nonspherical particles displayed higher margination and also higher retention, which led to their higher binding in comparison to nano-scale spherical particles [58].

3-4 Stability

Stability of particles in blood circulation is a key factor for achieving an organ-based drug delivery. In order to deliver drugs to the intended tissues, particles must avoid clearance by RES and filtration by lung, liver, or spleen. Particle size has a strong influence on clearance rate and stability. It has been reported that particles in the range of 20 nm and one μm have a low clearance rate, high circulation time, and stability [65].

Coating by zwitterionic structures is an effective strategy for evading uptake by RES and achieving more stability of particles. It has also been reported that coating te zwitterionic polymers on the surface of silver, gold, silica, and magnetite nanoparticles is a valid approach to improve biocompatibility and prolong circulation time [66]

On the other hand, PEGylation on the surfaces of particles can be an effective approach to prevent interactions with plasma proteins, reduce the macrophage uptake, prolong circulation half-life, decrease the accumulation of particles in the liver, and increase stability. PEG chains on the surface of nanoparticles create a hydrophilic barrier with a low charge and high chain flexibility, resulting in higher stability [67]

Particle shape should be considered as an effective factor in the stability of drug delivery nanoparticles in the blood circulation. More aspect ratio of the particles leads to less phagocytosis and longer circulation time and higher stability. Geng et al. showed that filomicelles remain in blood circulation about ten times longer than spherical particles [43]Gold nanorods had less accumulation in the liver in comparison to gold spheres, resulting in higher stability in the blood circulation and accumulation in tumors [55]. Moreover carbon nanotubes, worm-like iron oxide nanoparticles, paclitaxel-loaded filomicelles, and dextran-coated nano chains had longer circulation time, leading to more accumulation in tumor site and greater tumor shrinkage than spherical particles [56], [68], [69].

Heryadi et al. proved that shape stability of nonspherical nanoparticle is affected by complex manufacturing aspects. They showed that some particle properties such as porosity, surface roughness, hydrophobicity, and stiffness could affect shape stability [70].

3-5 Cytotoxicity

For in vivo applications, toxicity of drug deliver carriers should be precisely evaluated.

In addition to chemical composition, several other parameters, including carrier morphology, can also affect cytotoxicity, genotoxicity and inflammatory response, owing to the fact that particle shape plays a major role in cellular uptake as well as in intracellular behavior, and needless to say that the more likely a drug carrier can cross the cell membrane, the more likely it will cause mechanical or oxidative damages [3]. Researchers have investigated the effect of particle shape on its toxicity.

In an experimental study, hydroxyapatite nanoparticles were fabricated with similar sizes but different shapes including sphere, plate, needle and rod in order to evaluate the effect of shape on cytotoxicity and production of reactive oxygen species and inflammatory cytokines in immortalized human bronchial and immortalized mouse macrophage cell lines. Results showed that needle- and plate-shaped nanoparticles had induced more remarkable cell death compared to spherical and rod-shaped particles. Although spherical and rod-shaped particles represented a greater degree of cell uptake and particle-cell association, they induced the least cell death compared to other groups. It can be concluded that there is no relationship between particle-cell association and cytotoxicity, highlighting the considerable role of particle shape in cell death [71].

In another study, TiO2 particles were synthesized with similar sizes but different shapes, including spherical, dendritic, and spindle shapes. From cytotoxicity evaluation of these particles, it was concluded that dendritic and spherical particles induced the most and the least cytotoxicity, respectively. These results were believed to be due to the sharp edges of dendritic and spindle particles, considering that dendritic particles have higher edges than spindle particles [72].

These findings confirmed the data collected from two other studies which have demonstrated that SiC-based whiskers would cause cell death in hamster lung fibroblast cell line, whereas SiC spherical particles were shown to be nontoxic [73] and also fibrous Si3N4 induced the greater degree of cytotoxicity in bovine pulmonary macrophages compared to their particulate counterparts [74].

3-6 Biodistribution

Biodistribution of drugs and drug carriers is a crucial task in drug delivery systems, especially in cancer drug delivery. Recent studies proved that the particle shape of drug carriers affect their distribution and targeting. Nonspherical particles with their massive surface area to volume ratio are desirable for targeted drug delivery.
Generally, the passive targeting and accumulation of nanoparticles in tumor tissues are observable because of the enhanced permeability and retention (EPR) effect that can be useful in tumor therapy [75]. Thus it is reasonable to design nanoparticles that can escape from filtration by kidney, spleen, liver, and lung and clearance by the reticuloendothelial system to reach the target tissue [65]
Decuzzi et al. compared the murine biodistribution of silica particles with different shapes (spherical, cylindrical, discoidal, and quasi-hemispherical) and sizes (0.7-3 μm) [73]. The accumulation of discoidal particles in the lungs and heart is more than other particles, and the accumulation of them in the liver is less than other shapes because the elongated shapes can better evade phagocytosis of Kupffer cells [76].
An experiment compared the biodistribution of gold nanospheres and gold nanorods, and it was found that nanorods have less accumulation in the liver and more accumulation in tumor sites [55]. Park et al. investigated the targeting of iron oxide nano worms and nanospheres; they reported that nano worms have longer circulation and more accumulation in mice tumors [68], [69].
The biodistribution of mesoporous silica nanoparticles with two different shapes (aspect ratios, 1.5 and 5) have been studied. Long-rod mesoporous silica nanoparticles accumulated in the spleen; however, the short-rod nanoparticles distributed more in the liver [77].
Nonspherical carriers, especially elongated shapes, are very considerable for cancer drug delivery because these particles have less filtration in the liver, and the risk of hepatotoxicity will be decreased. An experiment investigated the circulation of filomicelles for cancer drug delivery and a high concentration of filomicelles into tumor-bearing micewas found which indicates low phagocytosis of elongated shapes and more circulation time. It should be considered that filomicelles accumulate less in healthy organs in comparison to tumor sites because of the easy entrance into tumors through small leaky vasculatures [56]. Chen et al. investigated a novel approach for the fabrication of bowl-shaped microparticles in order to oral delivery of curcumin to ulcerative colitis tissue. They showed that drug distribution in vivo is dependent on time, and drug accumulation in the colitis tissue was low in the first hours and increased after one day [78].
Besides the effects of particle shape, particle size and surface charge are also important in biodistribution. The nanoparticles with the hydrodynamic diameter less than 5.5 nm are rapidly excreted by kidney; also, the macrophages in the spleen and Kupffer cells in the liver remove the nanoparticles with a diameter larger than 200 nm [65], [79].

In addition, drug delivery to each organ needs specific nanoparticle design; for example, drug delivery for CNS disease needs nanoparticles with 20 nm that can pass through blood-brain and blood-retinal barriers [80].
All we described before was about passive targeting, but the particle shape is effective on active targeting either. Unlike small molecules, nanoparticles are able to display multiple ligands on their surfaces, which leads to ligand-receptor binding and avidity-based targeting [81].
The influence of nanoparticle size is obvious in ligand exhibiting, with increasing the particle size (for constant surface ligand density), the number of ligands, and finally, the bindings between the nanoparticle and cells will increase [38].
Anti-iCAM discs are internalized more slowly by endothelial cells than anti-iCAM spheres with the same sizes, whereas the discoidal particles have higher targeting specificity in mice [47]. Moreover, the number of specific bind interactions for targeted polystyrene nanorods are two folds higher than targeted nanospheres because they possess larger interfaces with an area of receptors [82].

4 Impact of particle shape on targeted drug delivery

4-1 Liver

The liver has several vital functions in the body, in particular, detoxification, protein synthesis, and helping the digestion process. Liver diseases such as liver cirrhosis, liver fibrosis, viral hepatitis, cholangiocarcinoma, and hepatocellular carcinoma lead to death annually. Efficient drug delivery to the liver is an outstanding goal in treatment of liver diseases [83].
The parenchymal cells of the liver are hepatocytes, and non-parenchymal cells are sinusoidal hepatic endothelial cells, Kupffer cells, and hepatic stellate cells. The purpose of liver drug delivery is transmitting the therapeutic agents to hepatocytes, however, in some cases, drug delivery to the non-parenchymal cells is the main target, and it depends on the disorder [84].
Enhanced permeability and retention (EPR) effect is the physiological mechanism of tumor accumulation of micro/nanoparticles. Accumulation of particles in the liver follows this mechanism either, and it can be an effective strategy for passive liver drug delivery [56]. In this method, the particles should scape from RES (which contains macrophages and phagocytes) and Kupffer cells in the liver. It is believed that the best range of size for particles that can be used in liver drug delivery is 50-250 nm [84]
Silicon-based particles with spherical, quasi-hemispherical, cylindrical, and discoidal shapes have been injected intravascularly into tumor-bearing mice. There was not any difference between the accumulation of spherical and quasi-

hemispherical particles in the liver; however, they accumulate about two times less than the cylindrical particles, and cylindrical particles accumulate about five times more than discoidal particles. Generally, the accumulation of spherical, hemispherical, and cylindrical particles in the liver was more than other organs like the brain, kidney, lung, tumor, spleen, and heart [76].

The liver uptake for nanospheres was significantly higher than nano chains with an aspect ratio of four with the same diameters [85].

Godin et al. indicated that discoidal porous silicon particles with 600 nm diameter and 400 nm thickness accumulate in the liver about two times more than other organs four hours following intravenous injection [86].

Spherical and rod-shaped gold nanoparticles with poly(ethylene glycol) (PEG) chains on the surface have been injected intravenously into ovarian tumor-bearing mice. The results showed that the accumulation of spheres in the liver is about four times more than rod-shaped particles after 24 hours, and generally, it was more than accumulation in other organs [55]

Kolhar et al. showed that the accumulation of rod-shaped polystyrene anti-transferrin receptor antibody-coated nanoparticles in the liver is less than the accumulation of spheres with the same characteristics, unlike other organs like spleen, kidney, heart, lung, blood, and brain [82].

PEGylated single-walled carbon nanotubes exhibit extra high accumulation in the liver in comparison to other organs [87].

Also, the surface modification can be a functional parameter for promoting the opsonization and increasing the phagocytosis. For instance, the opsonization by complement factors c3-c5 can target the particles to the Kupffer cells, which is not desirable for most of the liver drug delivery purposes [88].

Another approach is active targeting to the liver, and it will be possible with ligand-receptor interactions. There are several types of receptors on liver cells that have specific responsibilities including cell adhesion, transportation, and interaction with biomolecules. For instance, one of the receptors that exist on the surface of hepatocytes is asialoglycoprotein, which its ligands are galactose, lactobionic, and asialofetuin, and it can be a functional approach for drug delivery in the liver [83].

4-2 Spleen

Spleen targeting has significant clinical advantages in the diagnosis and treatment of diverse diseases, including spleen infections such as acquired immune deficiency (AIDS), leishmaniasis, and hematological disorders such as malaria, autoimmune hemolytic anemia, and hairy cell leukemia. Spleen targeting of drug carriers would be possible using unique anatomical-physiological characteristics of this organ, such as slower blood flow in its vasculature compared to the liver [89].

As discussed before, upon intravenous injection of carriers, they adsorb plasma proteins, which make them more visible for macrophages in the blood circulation and RES organs. Since the flow rates in spleen and liver are different, the distribution of injected carriers is non-uniform between these two tissues. About 85% of the carriers are phagocytosed by Kupffer cells in the liver, and only 15% of them may reach the spleen, and this issue is known as the most challenging problem for efficient spleen targeting [88]. Therefore, it would be desirable to design particles that could escape from Kupffer cells. Researches have shown that this goal is achievable via engineering particle physiochemical properties, especially their size, shape, and surface features [90].

In general, it has been shown that 200 nm to 3 μm is the optimal range of particle size for drug delivery to the liver and spleen. Within the aforementioned range, smaller particles are able to escape from phagocytic cells more efficiently compared to larger ones, probably because the quantity of proteins that have been absorbed on the surface of smaller particles is less than larger particles, and that may also explain why they possess longer circulation time [51], [91].

Particles coated with hydrophilic polymers such as polyethylene glycol (PEG) and polyethylene oxide, known as stealth particles, resists against opsonization, which leads to less recognition by phagocytic cells in the liver, resulting in higher particle concentration in the spleen [92], [93].

Particles with positive charge surfaces exhibit more tendency to phagocytosis compared to particles with a negative or neutral charge, probably because of the effect of surface charge on protein adsorption [94].

Carrier shape is also a crucial design parameter for splenic delivery. Nonspherical particles exhibit less uptake by Kupffer cells, likely due to the lack of formation of complete actin cup on their surface [39], [40].

In an experimental study, spherical and irregular shaped polymer lipid nanoparticles (LIPOMER) were synthesized, and their capability for spleen passive targeting was compared. Irregular-shaped particles exhibited more escaping from Kupffer cells, which led to a higher concentration of carriers in the spleen [95].

In another study, elongated and spherical poly (lactic-co-glycolic acid) (PLGA) particles were fabricated, and the effect of shape on macrophage uptake was evaluated in vitro. The results showed that elongated particles represent less phagocytosis than spherical counterparts [96].

4-3 Lung

Lung-targeted drug delivery systems have been designed to increase drug concentration in diseased tissue and subsequently reduce adverse effects in healthy organs in order to improve therapeutic efficiency in lung diseases such as asthma, local infections, tuberculosis, pneumonia, and lung cancer [97].

These systems can be administered to the body, either via pulmonary inhalation or intravenous injection. The inhalation route is a non-invasive route which is believed to provide efficient lung targeting, due to large surface area for drug absorption, avoiding the first-pass metabolism, and reducing systemic side effects [98].
This route also has the potential of systemic delivery of some medications such as insulin, probably due to large surface area, permeable endothelium, thin epithelium, and high blood supply [99], [100].
Inhaled drugs or drug carriers are usually cleared from the pulmonary tissue rapidly. Engineering the carriers can cause longer carrier retention in this tissue. It has shown that particle size plays an important role in particle stability in lung and also its targeting potential. Particles smaller than 1 μm mainly are removed by exhalation, while particles with diameter in the range of 1-5 μm mostly deposit in alveolar regions and known as the most optimal range and particles > 5 μm are readily removed by mucociliary mechanism [98].
It has been found that particle shape has a great impact on flowability, aerosolization and deposition properties of carriers which are determinant parameters in lung targeting through inhalation route [98].
Particle aerosolization depends on the van der Waals interactions between particles and walls of inhalation route or other particles which is related to particle features such as size, shape, surface morphology, and electrostatic properties [101].
Particles that have large contact areas such as elongated particles are not appropriate for lung targeting via this route due to large van der Waals forces between particles, which lead to more aggregation propensity [102].
In one study, particles with similar sizes but different shapes, including sphere, cube, plate, needle, and pollen, were fabricated in order to investigate the role of particle shape on flowability, aerosolization, and deposition properties of carriers. The results showed that pollen-shaped particles can be more suitable for inhalation drug delivery in comparison with other shapes, due to their better aerosolization, flowability, and deposition properties [101].
The intravenous route is another route that can be used for drug delivery to the lung using anatomo-physiological features of lungs including large endothelium and low blood circulation rate. In the case of active targeting, coupling carriers with ligands that are able to recognize lung endothelium markers would be a promising strategy.
Following intravenous injection, micro-particles larger than 7 μm exhibit rapid accumulation through physical entrapment in small capillaries of the lung [103].
In one study, Au-incorporated Au nanostructures with a similar size but different shapes including spherical, rod-shape, disc-shape, and cubic were injected into breast cancer-bearing murine EMT6, in order to investigate the role of shape in their in vivo fate [104]. It has been shown that Au nanocages displayed high pulmonary

accumulation compared to three other shapes; therefore, they were suggested to be promising in the treatment and diagnosis of lung diseases [104].
In an experiment, researchers have investigated the role of particle features, including shape, size, and surface chemistry on their circulation half-life, biodistribution and endothelial uptake. They synthesized polystyrene carriers with different shapes (spheres and elliptical discs) and sizes (0.1 to 10 μm). Since intercellular adhesion molecule 1 (ICAM-1) is overexpressed in the luminal surface of endothelial cells in many pathological conditions, the particles were functionalized with anti-ICAM antibodies in order to enhance their affinity to endothelial cells. This modification decreased their clearance rate from the circulatory system and increased their therapeutic efficacy [47].
Following intravenous injection, micron-size anti-ICAM coated spheres displayed nonspecific accumulation in the pulmonary vasculature probably because they had been trapped in small capillaries physically, but submicron size anti-ICAM coated spheres displayed fast and specific lung endothelial targeting [47].
Micron-size anti-ICAM coated elliptical discs displayed a prolonged blood circulation and specific endothelial targeting. Their prolonged circulation might be due to alignment with blood flow and reduced nonspecific conflict with the vessel walls, similar to the long circulation time of discoidal red blood cells. And their more specific targeting compared to micron-size spheres is likely due to their higher surface to volume ratio [47].
In another experiment, uncoated silicon-based particles with similar volumes but diverse shapes, including spherical, hemispherical, discoidal, and cylindrical forms, were fabricated and injected intravenously into tumor-bearing mice in order to evaluate the impact of particle shape on in vivo biodistribution. Assessment of the concentration of particles in the lung showed that discoidal particles have a higher concentration in the lung compared to other shapes [76].

4-4 Brain

These days, neurodegenerative diseases for instance Alzheimer, Huntington, and Parkinson are the most noticeable purpose of brain drug delivery [75].
The most important challenge in brain drug delivery is to overcome the blood-brain barrier (BBB) and reach neuronal tissues in the brain. Nanoparticles with controlled design can be useful in this field. Physiochemical characteristics of nanoparticles can affect cellular internalization, biodistribution, circulation, penetration into biological barriers, and finally, therapeutic effects in brain drug delivery. Delivery of the therapeutic components by nanoparticles can be done with intravenous or intranasal injection. In intravenous injection, nanoparticles escape reticuloendothelial system, then penetrate into the blood-brain barrier and finally target brain neuronal cells. In intranasal injection, nanoparticles utilize intracellular

transport and endocytosis mechanisms during movement through axons and then target to brain neuronal cells [75]

Ligand modification is one strategy for binding nanoparticles to endothelial cell surface receptors in the brain, including transferrin receptor and low-density lipoprotein receptor [105], [106]. For instance, in one study, modification with lactoferrin as a ligand which its receptor is expressed in neurons had good results with respects to number of nanoparticles and therapeutic agents in the brain [107].

Another strategy is the control of physiochemical properties like size, shape, and surface modification of nanoparticles for passing through BBB and reaching the neuronal tissue. At first, the nanoparticles must escape from eliminating processes of lung, liver, spleen, and kidney, and second, they must pass through BBB. Nanoparticles of around 150-300 nm can escape from filtration and pass through BBB either. Larger nanoparticles will be scavenged by reticuloendothelial systems, especially Kupffer cells in the liver and macrophages in the spleen [75], [108].

Rod-shaped polystyrene nanoparticles coated with anti-transferrin receptor antibodies accumulate in the brain about seven times more than the spheres with the same characteristics [82].

Accumulation of negatively charged gold nanoparticles after intravenous injection was insignificant, but it increased with decreasing the particle size from 5 nm to 1.4 nm [109].

Surface modification can be another approach for brain drug delivery using nanoparticles and targeting them to the brain tissue. Polysorbate 80-coated polybutylcyanoacrylate nanoparticles with different sizes (70, 170, 220, and 345 nm) were used for the delivery of methotrexate to the brain. Results indicated that coated particles with polysorbate 80 have more accumulation in the brain compared with uncoated counterparts. In addition, nanoparticles in 70 nm could improve the drug level in brain tissue while there were no noticeable differences between three other sizes [110].

4-5 Tumor

Nowadays, cancer is considered as one of the main causes of death all around the world. Numerous efforts have been made in cancer diagnosis and treatment, and remarkable advancement has been achieved [21]

Chemotherapy is almost the most important method in cancer therapy. One of the major causes of high mortality in cancer patients would be the inability to deliver drugs to the tumor site without causing adverse effects in other tissues. Hence, designing drug delivery systems that could reach to the tumor site and release their anticancer cargo in the target site would significantly improve therapeutic efficiency of the chemotherapy [111].

Nanomedicine can fulfill this goal by the fabrication of nanocarriers using various materials.

In order to achieve the optimal therapeutic efficiency, it is necessary to engineer physiochemical properties of drug carriers including chemical composition, size, shape and surface characteristics, according to the unique features of tumor tissues.

Numerous studies on tumor tissues have proved that tumor vasculature is different from the normal one. The high density of endothelial cells in normal vasculature and also the presence of tight junctions between them prevent particles or large molecules penetration through the vessel walls. In contrast, tumor vasculature has leaky walls with the gaps in the range of 100-800 nm between endothelial cells, which let nanoparticles with appropriate size diffuse through these gaps efficiently [112], [113].

Ineffective lymphatic drainage inside the tumor leads to the accumulation of penetrated particles in the tumor site. This phenomenon is known as the EPR effect, which is considered as the basis of passive targeting to tumor sites [112], [114]. EPR-based targeting is largely affected by particle properties that, among them, particle size has the greatest role. Obviously, only particles which are smaller than gap size are able to penetrate into the tumor interstitium. However, experimental evidence has shown that particles with sizes in the range of 30-200 nm are optimal for passive tumor targeting, likely due to rapid clearance of larger particles by the spleen and movement of smaller particles to the bloodstream followed by clearance by mononuclear phagocyte system (MPS) or kidneys [115].

The surface characteristics including surface charge or its functional groups are the other effective parameters on passive tumor targeting because they avoid protein adsorption, which leads to less uptake by phagocytic cells and longer circulation half-life [53].

It has been found that in addition to size and surface properties, particle shape also plays an important role in passive tumor targeting. Although spherical particles are showed to be promising candidates for cancer therapy, nonspherical particles bring some additional advantages [116].

It has been found that spherical particles are more likely to move along the streamlines. Hence, only particles that are adjacent to the vessel walls have the chance to extravasate into the tumor interstitium [117], whereas rod-shaped particles possess different hydrodynamic features leading to more instability along the streamline and therefore more propensity to move toward vessel walls. In addition, nonspherical particles have a larger surface to volume ratio compared to spherical particles with similar sizes, which leads to more tendency of particles for binding with the cells [118].

In an experiment, the effect of particle shape on tumor uptake and distribution was assessed. Gold nanostructures with similar sizes but various shapes, including

nanospheres, nanodiscs, nanocages, and nanorods were fabricated and injected intravenously to breast cancer-bearing mice. The results showed that spherical and disc-shape particles led to higher tumor uptake but less penetration tendency (mainly accumulate on the tumor surface) compared to cubic and rod-shape particles, which were distributed throughout the tumors instead of accumulation on the surfaces of the cancerous tissue. This behavior makes nanorods and nanocages suitable for photothermal cancer therapy [104].

In terms of circulation half-life, PEGylated Au nanospheres remained in the bloodstream longer than the others. Disc-shape and rod-shape particles displayed moderate and low circulation half-lives, respectively [104].

In a study conducted by Wang et al., liposomal nanodiscs and nanospheres were fabricated as paclitaxel carriers in treating prostate cancer, which is the most widespread cancer in males. These particles were modified with a particular peptide that was able to recognize fibronectin complexes, which are widely expressed in tumor stroma as well as tumor vessel walls. The results illustrated that nanodiscs displayed higher penetration and accumulation of their cargo at prostate tumor sites, which led to higher efficiency and lower toxicity [119].

In another experiment, hydroxyapatite nanotubes and nanospheres were fabricated as potential carriers for anticancer drugs, both hydrophobic drugs such as paclitaxel and hydrophilic drugs like doxorubicin hydrochloride. The results of this experiment showed that nanotubes displayed higher drug loading capacity, better cell internalization efficacy, and also higher retention capacity in comparison with nanospheres. In light of the results, scientists concluded that in addition to size and surface characteristics, the geometry of drug carriers would be a determinant factor affecting circulation time, cellular uptake, biodistribution, and targeted delivery [120].

5 Drug Release Profile

Drug loading capacity and drug release kinetic are crucial parameters in determination of the drug therapeutic efficiency. Zero-order kinetics is believed as the most favorable kinetics for drug delivery because the drug releases in a sustained manner over a more prolonged time in comparison with the administration of free drug [121]

In drug delivery systems, the drug may either absorb on the carrier's surface or be loaded in the interior zone. In the former case, the exterior surface area of the carrier, which greatly depends on its geometry, plays a major role in the efficiency of drug loading. Likewise, in the latter case, in which the drug is loaded inside the carrier such as hollow rod-shaped or tubular carriers like carbon nanotubes, drug loading efficiency greatly depends on the carrier shape [121].

It has been figured out that the drug release profile depends on several factors, such as interactions between drug and carrier, drug loading, and diffusion coefficient. Researchers have also assessed whether carrier geometry has a role in drug release profile or not. They prepared paracetmol loaded polyvinyl alcohol filaments by the hot-melt extrusion method, in order to use them in fused deposition modeling. Using the aforementioned technique, tablets have been fabricated in diverse geometries, including sphere, cube, cylinder, pyramid, and torus [122]
The dissolution rate showed that carrier geometry has a considerable effect on drug release behavior. The drug release rate from tablets with nearly the same surface area was in the following order; pyramid > torus > cube > sphere and cylinder. The required time for spheres and cylinders to release 90% of their loaded drugs (t90) was about 12h, while this time for pyramid was about 2h. This order is the same as the surface to volume ratio order of carriers, with spheres and pyramids possess the lowest and the highest surface to volume ratio, respectively [122].

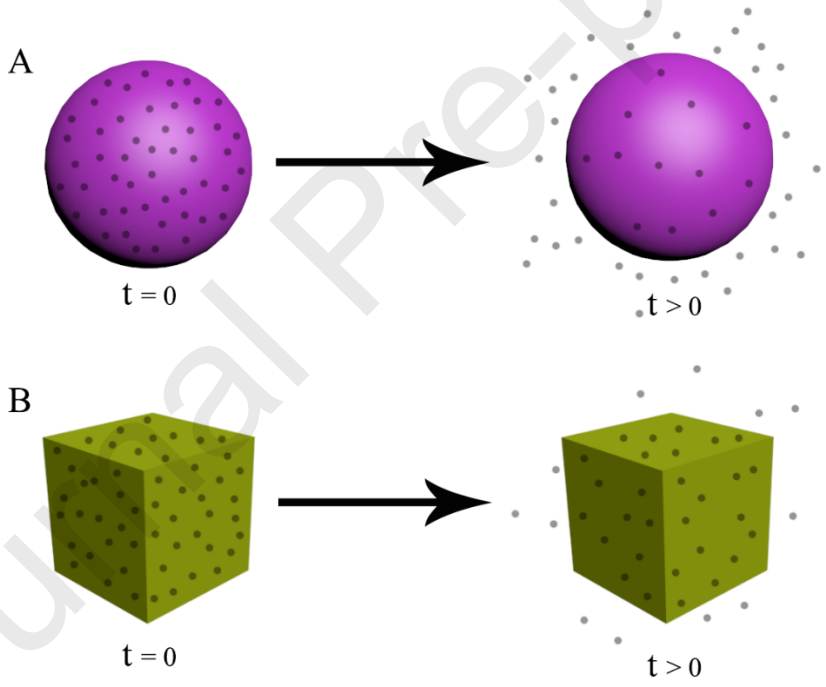

Figure 6 Schematic representation of drug release behaviors of spheres and cubes with the same surface to volume ratio: (A) higher drug release rate from spheres in comparison to cubes (B) with the same surface to volume ratio.

The drug release rate from tablets with almost the same surface to volume ratio was in the following order; sphere > cube > torus > cylinder > pyramid. The t90 values for all tablets except the pyramid were similar and in the range of 2-3h [122]. Figure

(6) indicates a schematic representation of the drug release behavior from different shapes and the same surface to volume ratio.

In another experiment, hydroxypropylmethylcellulose (HPMC) tablets were fabricated in different shapes such as flat-faced round, flat-faced beveled-edge, round concave, and oval in order to investigate the impact of tablet geometry on drug release profile. Drug release from tablets was controlled through the diffusion process. The data collected from this study represented that a larger surface area to volume ratio would lead to higher drug release rate, even if in tablet with the same surface area [123].

The impact of aspect ratio and surface area to volume ratio was also evaluated in another study using HPMC tablets. It can be concluded from the results that the higher the aspect ratio or surface area to volume ratio, the higher the drug release rate [124].

It can be concluded that it is possible to control the drug release rate from drug delivery systems by adjusting their shape.

6 Conclusion

This work focuses on the particle shape as one of the physical properties, which is considered to have a discernible role on the fate of drug-loaded particles through affecting their interactions with biological systems. Although mass production of nonspherical particles with uniform and precise shape and size still remains a challenge, there are several methods for the preparation of these particles in order to investigate the role of particle shape on drug delivery behavior. Some of these approaches, such as film stretching method, prepare nonspherical particles using their spherical counterparts, on the contrary, some other methods including self-assembling methods, microfluidics, and particle replication in non-wetting templates fabricate nonspherical particles using their constituent substances. A summary of nonspherical particles and their advantages compared with spherical particles is tabulated in the table (1).

Table 1 Summary of nonspherical particles with different shapes and their advantages in organ based drug delivery compared to spherical particles

Material	shape	Size	surface	Advantages	Ref
Gold	Spheres and rods	Spheres: 50 nm, rods: 10 × 45 nm	PEG	Nanorods displayed less uptake by macrophages, longer circulation time, higher tumor	[55]

				accumulation and less liver accumulation.	
	Spheres , rods, discs and cubes	769-817 nm	PEG	Spheres showed the longest circulation, lowest clearance by the RES and the highest overall tumor uptake.	[104]
Hydroxyapatite	Spheres, plates, needles and rods	70-127 nm	FITC	Spherical and rod-shaped particles induced higher particle-cell association and lesser cell death	[97]
TiO2	Spheres, dendrites and spindles	Spheres: 30-50 nm Spindles: 10-20 nm width, 50-100 nm length Dendrites: 40-70 nm width, 200-300 nm length	Al2O3 and ZrO2	Dendritic and spherical particles induced the most and the least cytotoxicity, respectively	[72]
PVA	Spheres, cubes, cylinders, pyramids and torus	Surface area/volume: spheres:0.634, cubes:0.866, cylinders: 0.854, pyramids:1.169, torus: 1.002	--------	Drug release rate from tablets with nearly the same surface area was in the following order; pyramid > torus > cube > sphere and cylinder	[122]

Hydroxypropylmethyl cellulose (HPMC)	Flat-faced round, flat-faced beveled-edge, round concave, and oval	Surface area to volume ratio 0.601-1.48 mm^2/mm^3	------	Larger surface area to volume ratio would lead to higher drug release rate	[123]
Hydroxyapatite, Calcium carbonate and calcium oxalate	Spheres, cubes, plates, needles, and pollens	3-24 μm	-------	Pollen-shaped particles displayed better aerosolization, flowability, and deposition properties more suitable for inhalation drug delivery in comparison to other shapes.	[101]
Silicon	Spheres, hemispheres, discs and cylinders	0.7-3 μm	-------	Discoidal particles had the highest accumulation in lung and heart, and the least accumulation in liver	[76]
Glyceryl Monostearate	Spheres and irregular shaped	329.25-444.65 nm	------	Irregular shaped particles exhibited better macrophage evading and higher accumulation in spleen	[95]
PLGA	Elongated particles and spheres	150 nm and 2 μm	PEG	Elongated particles represented less phagocytosis	[96]
Polyethylene glycol diacrylate (PEGDA)-based hydrogel	Discs and rods	Discs: diameter 80-220 nm, height 70-100 nm	-	Rod shaped particles displayed less cellular uptake by macrophages	[125]

		Rods: 100 × 100 × 400 nm and 100 × 100 × 800 nm			
Iron oxide	Worm-like paericles and spheres	Spheres: 30-40 nm Worm-like: 65-90 nm	Peptide	Nanoworms had longer circulation and more accumulation in mice tumor	[68], [69]
Mesoporous silica particles	Long and short rods	Diameter: 40-200 nm Aspect ratio: 1-8		Long-rod mesoporous silica nanoparticles accumulated in spleen however the short-rod nanoparticles distributed more in the liver	[77]
	Discs and spheres	Diameter: 500-2600 nm, height: 200-700 nm		Discoidal porous silicon particles accumulated in the liver about two times more than other organs.	[86]
Single-walled carbon nanotubes	Tubes and spheres	Diameter: 1–5 nm, Length:100–300 nm	PEG	Nanotubes exhibited extra high accumulation in the liver	[126]

In general, recent researches have shown that nonspherical carriers exhibit distinct behavior compared to spherical counterparts. For instance, it has been shown that nonspherical particles mostly exhibit longer circulation time likely via avoiding RES clearance. Alteration of particle shape also induces changes in cellular uptake and immune interactions due to alteration of particles' local curvature. Moreover, particles with different shapes possess different margination propensity due to their distinct hydrodynamic behavior. They also exhibit different drug release profiles and

active targeting, which both depend on the surface area that is related to particle shape. It has also been discussed that in addition to other physiochemical properties such as size and surface chemistry, controlling the particle shape could affect its biodistribution.

It can be concluded that it is not possible to choose a shape for drug delivery carriers as the most appropriate shape to achieve the highest tissue targeting efficiency. In fact, the optimum shape can be different based on the target tissue. Sometimes, the goal is reaching a prolonged circulation time and escaping from RES organs; in these cases, for instance, using rod-shaped particles instead of spherical ones might be a better choice. On the other hand, sometimes, one of these RES organs, such as lung is the target tissue; in these cases, the discoidal shape might be the most appropriate shape. By engineering particle shape as well as the size and surface chemistry with regard to a target tissue, greater particle accumulation in the target site, and subsequently, higher therapeutic efficacy can be achieved. Nevertheless, many more studies on various shapes and their role in biodistribution are needed in order to determine the best shape for tissue targeting more confidently.

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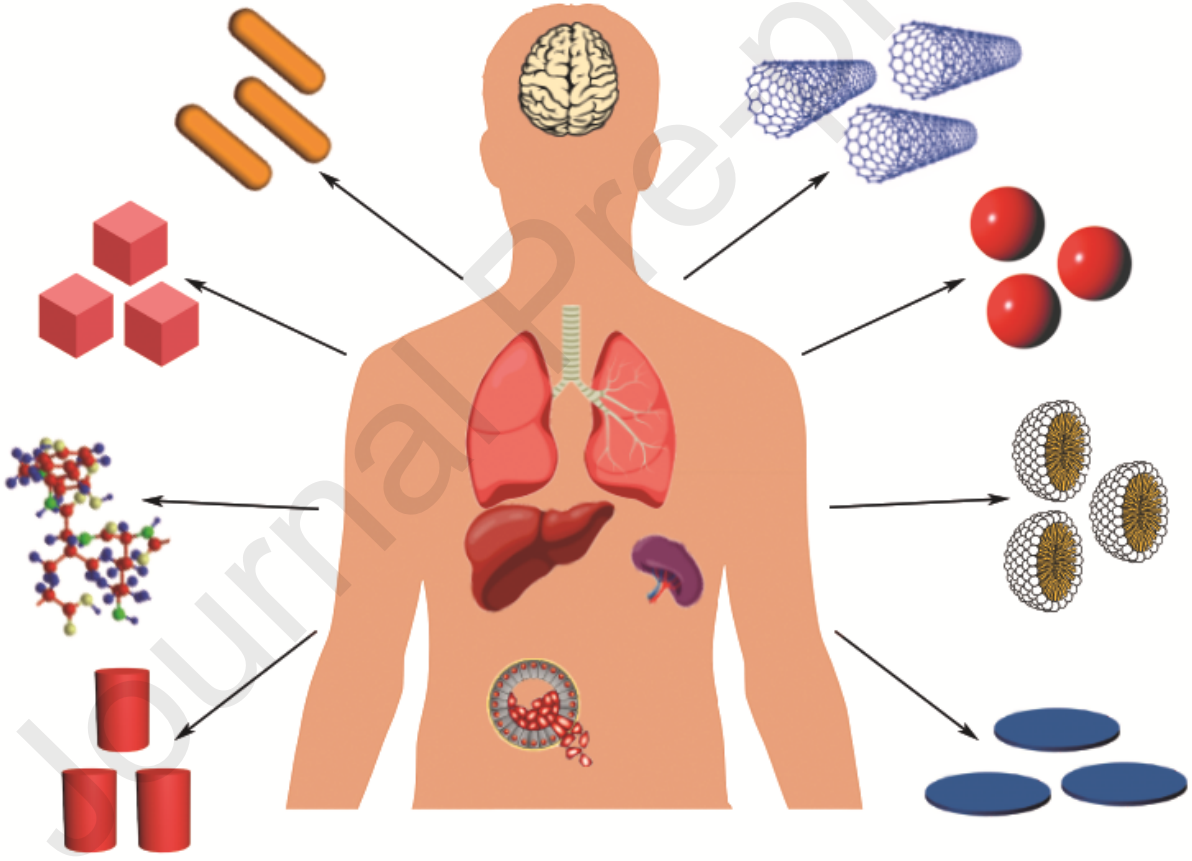

Particle geometry is an effective parameter in organ based drug delivery

Highlights

1. Particle geometry has an important role on drug delivery system.
2. Nonspherical carriers exhibit distinct behaviors compared to spherical counterparts.
3. Particles with different shapes have different behaviors in each organ.

Conflict of interest

The authors declare that there is no conflict of interest regarding the publication of this article.