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Review

The effect of particle shape on cellular interaction and drug delivery applications of micro- and nanoparticles

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ABSTRACT

Encapsulation of therapeutic agents in nanoparticles offers several benefits including improved bioavailability, site specific delivery, reduced toxicity and *in vivo* stability of proteins and nucleotides over conventional delivery options. These benefits are consequence of distinct *in vivo* pharmacokinetic and biodistribution profile of nanoparticles, which is dictated by the complex interplay of size, surface charge and surface hydrophobicity. Recently, particle shape has been identified as a new physical parameter which has exerted tremendous impact on cellular uptake and biodistribution, thereby *in vivo* performance of nanoparticles. Improved therapeutic efficacy of anticancer agents using non-spherical particles is the recent development in the field. Additionally, immunological response of nanoparticles was also altered when antigens were loaded in non-spherical nanovehicles. The apparent impact of particle shape inspired the new research in the field of drug delivery. The present review therefore details the research in this field. The review focuses on methods of fabrication of particles of non-spherical geometries and impact of particle shape on cellular uptake, biodistribution, tumor targeting and production of immunological responses.

1. Introduction

Nanoparticles have reformed pharmaceutical and drug delivery field by shifting paradigm towards the targeted drug delivery. Encapsulation of drugs into nanoparticles offers several advantages including improved bioavailability (Benival and Devarajan, 2012), site specific delivery (Alibolandi et al., 2016), reduced toxicity (Olson et al., 2015) and *in vivo* stability of macromolecules such as proteins (Varamini and Toth, 2016) and nucleotides (He et al., 2015a,b). It is well established that nanoparticles follow distinct pharmacokinetic and biodistribution pattern after *in vivo* administration, which is dictated by the complex interplay of size, shape, surface charge and surface hydrophobicity.

Physicochemical properties of nanoparticles including size and surface properties in association with physiological processes including phagocytosis, splenic filtration and renal excretion contribute significantly in dictating *in vivo* fate of nanoparticles. For instance, small particles (≪30 nm) are excreted through the kidney (Moghimi et al., 2001), while comparatively larger particles (30–150 nm) are sequestered in the bone marrow (Moghimi, 1995). However, the same particle size range led to the accumulation of particles in tumor tissues due to Enhanced Permeation and Retention (EPR) effect when biodistribution was studied in tumor bearing animal models (Saisyo et al., 2016). For example, cisplatin loaded polymeric micelles (102 nm) exhibited 5-fold enhanced tumor uptake as compared to free drug in mice after intravenous administration (Saisyo et al., 2016). Particles ≫ > 200 nm were taken up by the macrophages and targeted to the reticuloendothelial system (Li et al., 2011). Additionally, macrophage uptake of nanoparticles was also seen to be dependent on particle size (Ayhan et al., 1995; Champion et al., 2008; Hirota et al., 2007; Koval et al., 1998; Pacheco et al., 2013; Tabata and Ikada, 1988). Moreover, nanoparticle size also affected cellular uptake efficiency and kinetics (Dong and Irudayaraj, 2012), internalization mechanism (Mironava et al., 2010; Rejman et al., 2004) and intracellular distribution (Huang et al., 2012; Oh et al., 2011). In addition to the size, surface hydrophobicity also influenced *in vivo* biodistribution of nanoparticles. Particles with hydrophilic surfaces escaped phagocytosis and exhibited longer circulation half life (Ishihara et al., 2012; Otsuka et al., 2012; Storm et al., 1995; Torchilin and Trubetskoy, 1995). Depending upon the size, long circulating nanoparticles can be targeted to the tumor (Han et al., 2015; He et al., 2015a,b; Saw et al., 2015) and spleen (Klibanov et al., 1991; Moghimi et al., 1993, 1991; Peracchia et al., 1999). For example, PEGylated polycyanoacrylate nanoparticles (≫ > 200 nm) accumulated in the spleen with reduced hepatic accumulation, probably due to modification of plasma protein adsorption pattern whereas paclitaxel loaded folate conjugated poly(lactic-co-glycolic acid)-polyethyleneglycol nanoparticles (≪200 nm) exhibited improved therapeutic efficacy against endothelial carcinoma due to

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enhanced tumor concentration of nanoparticles (Liang et al., 2011). High tumor uptake of nanoparticles could be due to enhanced permeation of nanoparticles through leaky vasculature of tumor cells while high spleen uptake was probably due to physical filtration of particles within endothelial space of the sinusoidal spleen. However, splenic concentration of PEGylated nanoparticles in tumor bearing animal models was not studied. Surface charge is also known to affect *in vivo* journey of nanoparticles. It is well accepted that neutral or negatively charged nanoparticles are less likely to be taken up by the cells as compared to positively charged nanoparticles. For instance, highly positively or negatively charged PEG-oligocholic acid based micellar nanoparticles exhibited enhanced uptake by the RAW 264.7 murine macrophages cell line after opsonisation *in vitro* and high liver uptake *in vivo* while slightly negative charged nanoparticles exhibited enhanced tumor uptake and low liver uptake (Xiao et al., 2011). Dendritic cell uptake of polystyrene particles was also affected by the surface charge. Particles ≪500 nm were more efficiently taken up by the dendritic cells as compared to larger particles. However, uptake of large particles increased when surface charge was positive (Foged et al., 2005).

After the size and surface properties, particle shape has been identified as an important physical parameter which has shown tremendous impact on *in vivo* performance of nanoparticles by altering cellular uptake, cellular functions and biodistribution. While the impact of particle shape on *in vivo* journey of nanoparticles and ultimately on targeting to cancer sites has been illustrated recently in a review published by Toy R et al. (Toy et al., 2014), the major focus is shape effect on cancer nanomedicine. Another review focuses on methods of fabrication of mesoporous silica nanoparticles of non-spherical geometry and their drug delivery applications (Hao et al., 2016a) has also been published recently. Major progressions in the area of particle shape effect on drug delivery have also been reviewed by other research group (Mathaes et al., 2015), although briefly.

The present review entails, a detailed discussion on cellular interaction, biodistribution and circulation half life and antitumor efficacy of non-spherical nanoparticles. The review also focuses on methods of fabrication and characterization of micro-/nanoparticles of non-spherical geometry.

2. Methods of fabrication of non-spherical particles

Methods of fabrication of drug loaded spherical micro-/nanoparticles including nanoprecipitation, solvent evaporation and emulsion solvent diffusion have extensively been explored and reviewed in detail (Vauthier and Bouchemal, 2008). The impact of particle shape on *in vivo* performance of nanoparticles has inspired fabrication of particles of different geometries. PRINT (Perry et al., 2011) and microfluidics (Xu et al., 2005) techniques have been used for fabrication of non-spherical particles for drug delivery application. Film stretching method involves manipulation of shape of the spherical particles to fabricate non-spherical particles of different geometries (Champion and Mitragotri, 2006). Standard methods including modified nanoprecipitation and solvent evaporation have also been adapted for design of asymmetric/non-spherical particles. Table 1 summarizes properties of non-spherical nanoparticles fabricated by different methods.

2.1. Particle Replication In Nonwetting Templates (PRINT):

PRINT is a top down fabrication technique for generation of micro and nanoparticles of different sizes and shapes. It has been used for fabrication of non-spherical particles of different geometries including cube (Kelly and DeSimone, 2008; Parrott et al., 2010; Petros et al., 2008), cylindrical (Galloway et al., 2013; Gratton et al., 2007), rod (Fromen et al., 2015), hexnuts (Parrott et al., 2010) and donut (Khodabandehlou et al., 2015). PRINT process involves the generation of elastomeric fluoropolymer-based flexible PRINT molds by wetting the silicon wafer with a liquid polymeric precursor which produces micro/nano sized cavities. These cavities are filled with liquid preparticle material by using lamination based approach which is then converted into a solid particles by either photocuring or solvent evaporation. These solidified particles are removed from the cavities using an adhesive layer which are then obtained by dissolving the adhesive layer (Caldorera-Moore et al., 2010). Drug delivery applications of PRINT particles have been reviewed elsewhere in detail (Beletskii et al., 2014; Perry et al., 2011). PRINT technology was reported for the fabrication of particles of wide size range from 80 nm–20 μm, which was comprised of different matrix materials including polymers (Euliss et al., 2006), hydrogels (Petros et al., 2008) and proteins (Kelly and DeSimone, 2008). This technique has also been used for design of polyethylene glycol based nanoparticles for delivery of anticancer agents (Wang et al., 2010).

2.2. Microfluidic

In this technique, non-spherical micro/nanoparticles are fabricated by formation and shaping of monodisperse liquid droplets in microfluidic device subsequently solidification of droplet via *in situ* polymerization or lowering the temperature. The method is suitable for the fabrication of monodisperse colloid particles of materials of wide nature including gels, liquids, polymers and metals. This technique provides precise control over size and shape thereby able to generate monodisperse systems. Fabrication of spheres, disks and rods with size from 20 to 1000 μm using microfluidic device has been reported (Xu et al., 2005). Bullet shaped particles have also been prepared by using this technique (Hakimi et al., 2014). In microfluidic system, particle shape and size can be changed by controlling the flow rate of the continuous phase (Riahi et al., 2015). Particle size was found to be decreased with decrease in flow rate while gradual increase in the flow rate of continuous phase resulted in the formation of toroidal particles (Wang et al., 2009a). Furthermore, material attributes including polymer concentration, chemical nature and molecular weight were also found to be exerted profound impact on particle geometry (Wang et al., 2009a).

2.3. Film stretching method

In film stretching method, spherical particles are used as a base and are stretched in particles of different shapes. Film stretching method has been reported for the design of polystyrene based non-spherical particles of different geometry including worm like, oblate ellipsoids, prolate ellipsoids, elliptical disks, rectangular disks and UFO-shaped (Fig. 1) (Champion and Mitragotri, 2009, 2006). Spherical particles were added to viscous solution preferably containing polyvinyl alcohol and suitable plasticizer. Films were casted from the above solution which subsequently stretched using a custom made apparatus. Degree of stretching was found to be the detrimental factor of the dimensions of particles while experimental conditions influenced the particle shape during stretching. For instance, polystyrene based spherical particles were stretched in oil at 120 °C to produce needle shape while elliptical discs were obtained by stretching spherical polystyrene particles in toluene at room temperature (Doshi and Mitragotri, 2010). Furthermore, physical properties such as film thickness and solution viscosity also influenced the geometry of non-spherical particles. For instance, depending upon the viscosity, particles can have either pointy or flatter ends. Additionally, thin films were resulted in the formation of flatter particles. (Champion et al., 2007a,b; Champion and Mitragotri, 2006). In addition to polystyrene, PLGA based spherical particles were also stretched to fabricate elliptical disks (Fig. 2) (Yoo and Mitragotri, 2010). Film stretching method therefore can be used for design of non-spherical particles of both non-biodegradable and biodegradable polymers with a wide array of defined geometries.