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Editorial

In Drug Delivery, Shape Does Matter

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Design and engineering of novel carriers for drug delivery has long been an area of active research (1). Numerous studies have been reported on engineering carriers for encapsulation of drugs, release, biocompatibility, clearance, and targeting. Researchers have long sought to define key design parameters that govern the performance of drug delivery carriers. Two parameters in particular, size and surface chemistry have been extensively studied. Several general guidelines have been established to guide the selection of size and surface chemistry to achieve the desired response. For example, nanoparticles with diameters less than 100 nm are considered suitable for tumor targeting via leaky vasculature (2). On the other hand, large microspheres (d>40 μm) have been used as embolizing agents. Various guiding principles have also been established for selection of surface chemistry. For example, immobilization of polyethylene glycol on particles has been shown to reduce protein adsorption and phagocytosis (3). On the other hand, immobilization of peptides has been used to target particles to various organs (4). Optimization of surface coating for balancing stealth *vs.* targeting properties has also been reported (5).

In the last few years, however, there has been growing recognition that particle properties other than size and surface chemistry can be engineered for the purpose of drug delivery (6–9). Among them, shape represents an important particle parameter. There already exist several examples of how shape of carriers can be controlled to enhance the performance of drug delivery carriers. Recent studies performed using particles of different shapes have shown that phagocytosis by macrophages exhibits a strong dependence on shape (10). At a smaller length scale, Gratton *et al*. demonstrated that internalization of cylindrical particles exhibits a strong dependence on their aspect ratio. Specifically, particles with an aspect ratio of three were internalized about four times faster than their spherical counterparts of the same volumes (11). Counter examples of dependence of internalization on shape also exist (8). It is possible that the precise dependence of internalization on shape depends on the interplay between several other parameters. Particle shape has also been shown to influence carrier behavior *in vivo*. Specifically, Geng *et al*. (8) have shown that long cylindrical micelles exhibit long circulation and high tumor targeting compared to their spherical counterparts. More recently, Muro *et al*. (9) compared biodistribution of spherical and disk-shaped particles and reported that large elliptical disks exhibited higher targeting efficiency compared to spheres. One thing is clear; shape has a profound impact on performance of drug carriers.

This theme issue is dedicated to the role of carrier shape in drug delivery. Three contributions describe various aspects of the role of shape in drug delivery. The first manuscript by Champion and Mitragotri reports the impact of shape on phagocytosis. Specifically, they report that long, worm-shaped particles exhibit negligible phagocytosis compared to spherical particles of equal volume. The authors suggest that reduced phagocytosis is a result of decreasing high curvature regions of the particle to two single points, the ends of the worm-shaped particles. The second contribution by Gratton *et al*. reports on endocytosis of shape- and size-specific particles as a function of zeta potential in different cell types. Using a top-down particle fabrication technique called PRINT, the authors fabricate monodisperse 1 μm cylindrical particles and report that cylindrical 1 μm particles are readily internalized into various cells without toxicity. The third contribution analyzes the role of particle geometry (size and shape) at the tissue and cellular scale. Decuzzi and Ferrari compare predictions of mathematical models and observations from *in vitro* experiments to show the relevance of particle geometry in systemic delivery.

The field of "shape engineering" of drug delivery carriers is still in its infancy. However, the existing literature on this topic, regardless of its small size, clearly indicates the merits of exploring shape as an important parameter and hints at the exciting prospects of this field.

INTERVIEW WITH DR. SAMIR MITRAGOTRI

1. *What do you think holds the key to your success as a pharmaceutical scientist*?

Success is made possible by people. I have been fortunate to have excellent mentors, students and collaborators.

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2. *What do you consider to be your key research accomplishments*?

We have developed ways to enhance transdermal and transmucosal delivery of macromolecules. Our particular contribution has been on developing physical and chemical means to permeabilize skin and mucosal membranes. We have also developed strategies to prepare micro/nanoparticles of various shapes and used them to understand the role of geometry in particulate drug delivery. We have also made contributions to mathematical modeling of transport processes in the body including permeation across the skin, intracellular trafficking in cells, and permeabilization of cell membranes. These models have enhanced our understanding and enabled new applications in some cases.

3. *What was the turning point in your career*?

Joining Prof. Langer's laboratory as a graduate student. That was my first exposure to research and it shaped my outlook on science and academic career.

4. *Who are the individuals who most influenced your research career*?

Many people have influenced aspects of my career but two in particular. My father who kindled my liking for engineering at an early age and Bob Langer who inspired me and introduced me to research.

5. *Pharmaceutical scientists are faced with the dilemma of having to publish in biomedical or basic science journals. Does it mean cutting edge science will not likely be featured in the Pharmaceutical Research*?

Not necessarily. Choice of journal depends on the targeted audience. I see the need to publish in a variety of journals including engineering, pharmaceutical, biomedical and multidisciplinary journals. Diversification of journals is essential to foster inter-disciplinary communication and collaborations.

6. *Where is the field of Engineering Carriers of Novel Shapes for Drug and Nucleic Acid Delivery going? How do the articles in the theme section fill the gap*?

The field is still in infancy but off to a great start. Researchers are just beginning to appreciate that shape can have a profound influence on the behavior of drug delivery carriers. The articles in this theme section clearly demonstrate this point. These articles will add to our understanding of how shape matters and will inspire future studies to advance our understanding.

7. *What are the challenges for Engineering Carriers of Novel Shapes and how can be overcome*?

There are several challenges. Perhaps the most significant challenge is in understanding the role of shape. Upon administration in the body, drug delivery carriers have to overcome several hurdles including uptake, clearance, degradation, non-targeted accumulation, and phagocytosis prior to delivering the therapeutic payload. The ability of carriers to overcome these hurdles is likely to depend on shape. Such dependencies must be understood. The role of shape is also likely to depend on other key parameters such as size and surface chemistry. Such interdependencies also pose a challenge in terms of developing an understanding. Another challenge is development of technologies to produce particles of various shapes using biocompatible materials. Great strides have already been made towards this goal.

8. *What is the key to developing successful collaborative relationships*?

Good interactions between people. A genuine desire to interact with the collaborators at multiple levels is essential for a successful collaboration.

9. *What is your philosophy of educating graduate students*?

Research is a means of turning graduate students into creative and independent scientists. My goal is to facilitate this transition and do whatever it takes to make it happen. My precise role varies depending on the student. In general, I always encourage them to think of the big picture and innovate.

10. *What are the challenges facing the pharmaceutical sciences*?

Drug delivery continues to be a challenge in the field. Many of these challenges have been identified and significant progress has been made in the last couple of decades to address them. New discoveries have been made to facilitate the delivery of proteins, peptides and nucleic acids. One challenge now is to convert these discoveries into successful clinical therapies that will help patients.

11. *What is the place for collaboration with industry in academia*?

Industrial collaborations play an important role in academia, especially in the field of drug delivery. Researchers are really motivated to see their discoveries and inventions reach patients and collaboration with industry is a natural step along the way.

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