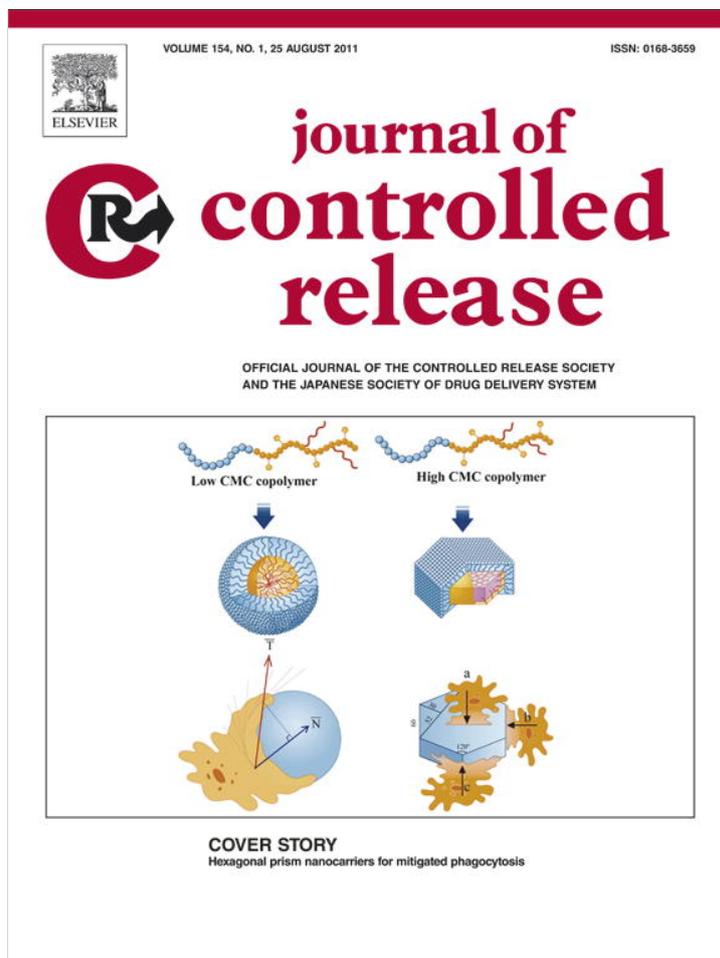


Provided for non-commercial research and education use.
Not for reproduction, distribution or commercial use.



This article appeared in a journal published by Elsevier. The attached copy is furnished to the author for internal non-commercial research and education use, including for instruction at the authors institution and sharing with colleagues.

Other uses, including reproduction and distribution, or selling or licensing copies, or posting to personal, institutional or third party websites are prohibited.

In most cases authors are permitted to post their version of the article (e.g. in Word or Tex form) to their personal website or institutional repository. Authors requiring further information regarding Elsevier's archiving and manuscript policies are encouraged to visit:

<http://www.elsevier.com/copyright>



Contents lists available at ScienceDirect

Journal of Controlled Release

journal homepage: www.elsevier.com/locate/jconrel

Cover Story

Hexagonal prism nanocarriers for mitigated phagocytosis

One of the key elements for successful delivery of particulate drug formulations to the target sites is to prolong the blood circulation by escaping phagocytosis by macrophages of the reticuloendothelial system (RES). It has been well established that PEGylation of particles increases the blood circulation time. (PEGylated particles have longer circulation time relative to the control. The majority of the PEGylated particles are still cleared from circulation after several hours, and only less than 10% of the total particles may circulate after 10 h.) It was also known that the particle shape affects blood circulation. Only recently, the effects of particle shape and size on phagocytosis were examined as a result of the ability to control the particle properties. Sharma et al. demonstrated that microparticles of prolate ellipsoids were better than spherical particles in prolonging the blood circulation because of less efficient phagocytosis by macrophages in the RES [1].

In an article published in this issue Professor Hsiue and his team examined the phagocytosis phenomenon in more detail using polymer micelles of spherical and hexagonal shapes [2]. Their research proposes a new strategy for mitigating phagocytosis and extending blood circulation after drug carriers are introduced into bloodstream. The shape of drug carriers was found to strongly affect the process of phagocytosis by the mononuclear phagocytic system. When macrophage contacts a particle, there exists a specific angle Ω between the cell and particle surface. The Ω is the angle between vector N and T shown on the cover figure. N is normal to the membrane at the site of attachment and T is average of tangential angles from 0° to $\pi/2$. The data has shown that drug carriers having a specific shape, characterized by the Ω angle $>45^\circ$, can evade the immune system more efficiently than the spherical particles. Naturally, more hexagonal nanoparticles remained in blood than the spherical particles (14% vs 2%) after 10 h. An interesting approach here is that the shape of the polymeric micelles was controlled by the critical micelle concentration (CMC) of the copolymer. The CMC alters the interfacial energy of micelles by removing the hydrophobic interaction between the copolymer and the loaded drug, resulting in a

unique geometric shape, either hexagonal or spherical nanoparticle. For hexagonal nanoparticles of $120\text{ nm} \times 104\text{ nm} \times 21.6\text{ nm}$ there are three Ω values along the major axis, side flat, and top flat of hexagonal prime of 40.9° , 49.1° and 78.2° , respectively. These values corresponded with significant spreading of cells but not internalization.

Although further studies are necessary to obtain full understanding of the effects of particle size and shape, it is clear that the particle properties have profound influence on phagocytosis. Current advances in nanofabrication can undoubtedly produce nanoparticles of various sizes and shapes as necessary. This in turn will produce nanoparticles delivering the loaded drug to the target site more efficiently. In another article in this issue, Professor Dufès and her team showed highly efficient tumoricidal activity of tocotrienol-loaded transferrin-bearing vesicles [3], and such vesicles may become even more promising therapeutic tool, if engineered to form a specific shape. Further research on particle shape and size is expected to bring a new dimension to targeted drug delivery.

References

- [1] G. Sharma, D.T. Valenta, Y. Altman, S. Harvey, H. Xie, S. Mitragotri, J.W. Smith, Polymer particle shape independently influences binding and internalization by macrophages, *J. Control. Release* 147 (2010) 408–412.
- [2] S.-Y. Lin, W.-H. Hsu, J.-M. Lo, H.-C. Tsai, G.-H. Hsiue, Novel geometry type of nanocarriers mitigated the phagocytosis for drug delivery, *J. Control. Release* 154 (2011) 84–92.
- [3] J.Y. Fu, W. Zhang, D.R. Blatchford, L. Tetley, G. McConnell, C. Dufès, Novel tocotrienol-entrapping vesicles can eradicate solid tumors after intravenous administration, *J. Control. Release* 154 (2011) 20–26.

Kinam Park
Purdue University,
Departments of Biomedical Engineering and Pharmaceutics,
West Lafayette, Indiana, USA
E-mail address: kpark@purdue.edu.