Journal of Controlled Release 239 (2016) 249

Contents lists available at ScienceDirect

Journal of Controlled Release

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

Cover story

Hemocompatible and immune-safe library of citrem-phospholipid liquid crystalline nanoplatforms

Liposomes have been used as efficient drug carriers for more than several decades. Recently, lyotropic non-lamellar liquid crystalline (LC) nanodispersions consisting of internally self-assembled nanoparticles (e.g., cubosomes and hexosomes) have received attention as an alternative platform for drug delivery, imaging, and design of diagnostic modalities [1]. In particular, they are attractive for development of injectable carriers for accommodating poorly water soluble drugs, hydrophilic peptides, and diagnostic agents. Some LC nanodispersions, however, are known to have poor hemocompatibility including hemolysis and complement activation [2], and potential toxicity of certain lipid/amphiphile constituents [1,2]. This limits their use as drug delivery vehicles for intravenous (I.V.) administration.

The development of non-lamellar LC aqueous nanodispersions as safe and efficient I.V. drug carriers requires a mechanistic and interdisciplinary approach focusing on the formation of nanoparticles composed of naturally occurring lipids that are structurally stable in human plasma, fully hemocompatible, and capable of solubilizing various drugs. Accordingly, the use of a naturally occurring biodegradable lipid such as phosphatidylcholine (PC) remains a viable option as a promising safer amphiphile. Overcoming the strong tendency of PC to form lamellar phases, however, is challenging and requires the addition of other biologically relevant lipids or an apolar non-toxic solvent modifier [3].

A paper in this Issue by complimentary research teams of Dr. Yaghmur and Professor Moghimi [4] addresses the raised concepts and limitations in the LC field. They introduce a versatile library of self-assembled lamellar and non-lamellar LC nanoparticles composed from two biologically compatible components: soy phosphatidylcholine and citrem. Citrem is an anionic citric acid ester of monoglycerides, and it has been approved by the United States Food and Drug Administration as an emulsifying agent in food products. It also has anti-oxidative properties. The nanoparticles' self-assembled interior is sensitive to lipid composition and increasing the citrem concentration induces the formation of lamellar/non-lamellar LC and micellar nano-assemblies. The structural diversity was spanned into four distinct phases: L_α, V_2, H_2, and L_2 leading to colloidal transformation from vesicles *via* cubosomes and hexosomes to an emulsified L_2 phase (ELP), respectively.

The morphological and structural features of the citrem-phospholipid library were thoroughly characterized through an integrated approach involving synchrotron small-angle X-ray scattering (SAXS), cryogenic transmission electron microscopy (cryo-TEM), and nanoparticle tracking analysis (NTA). There are five unique features with this initiative. First, this strategy has overcome the need for a secondary emulsifier, which is necessary to achieve colloidal stability for non-lamellar LC aqueous dispersions. Second, the described binary system could also be produced with low energy input, and without the use of an organic hydrotropic solvent. This is highly advantageous for encapsulation of temperature-sensitive and/or solvent-labile biopharmaceuticals. Third, citrem conferred stability to these nanodispersions in human plasma. Fourth, the LC nanodispersions, regardless of their internal nanoarchitectures, were hemocompatible and did not trigger complement activation, presumably due to surface interactions with the complement regulatory protein factor H. The latter is important from the immune safety point of view, since inadvertent complement activation could contribute to adverse injection-related reactions with cardiovascular, bronchopulmonary, mucocutaneous, neuropsychosomatic, and autonomic manifestations. Finally, by varying citrem to PC weight ratio, macrophages responded differently in nanodispersion recognition and uptake. Therefore, this approach opens opportunities both for macrophage targeting as well as by-passing macrophage recognition.

In summary, this work [4] is a welcome addition to the arsenal of functional, yet, simple drug delivery systems. Their attractiveness is linked to their simple design, tunable nanostructural versatility, hemocompatibility, innate immune safety, and their potential capability of solubilizing and sustaining the release of amphiphilic, hydrophobic and hydrophilic drugs. In addition to these, citrem may prove to become an effective candidate for surface engineering of other nanoparticulate delivery systems against complement activation. It will take some time before the usefulness and the promises of the citrem:PC system can be realized when the drug loading and drug release profiles are optimized for clinically useful indications. More systematic research on the physicochemical properties of LC, and how they affect the drug release profile is necessary. The work by the Yaghmur-Moghimi team presents a new step toward achieving the full understanding of the LC system for clinical applications.

References

[1] I.D.M. Azmi, S.M. Moghimi, A. Yaghmur, Cubosomes and hexosomes as versatile platforms for drug delivery, Ther. Deliv. 6 (2015) 1347–1364.
[2] I.D. Mat Azmi, L. Wu, P.P. Wibroe, C. Nilsson, J. Østergaard, S. Stürup, B. Gammelgaard, A. Urtti, S.M. Moghimi, A. Yaghmur, Modulatory Effect of human plasma on the internal nanostructure and size characteristics of liquid-crystalline nanocarriers, Langmuir 31 (2015) 5042–5504.
[3] I. Martiel, L. Sagalowicz, R. Mezzenga, Phospholipid-based nonlamellar mesophases for delivery systems: Bridging the gap between empirical and rational design, Adv. Colloid Interf. Sci. 209 (2014) 127–143.
[4] I.D.M. Azmi, P.P. Wibroe, L.-P. Lu, A.I. Kazem, H. Amentisch, S.M. Moghimi, A. Yaghmur, A structurally diverse library of safe-by-design citrem-phospholipid lamellar and non-lamellar liquid crystalline nano-assemblies, J. Control. Release 239 (2016) 1–9.

Kinam Park
Purdue University
Departments of Biomedical Engineering and Pharmaceutics
West Lafayette, IN 47907, USA
E-mail address: kpark@purdue.edu

http://dx.doi.org/10.1016/j.jconrel.2016.09.005