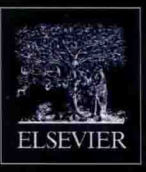

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Stable Nanoemulsions

Self-Assembly in Nature and Nanomedicine

Joseph D'Arrigo

Stable Nanoemulsions: Self-Assembly in Nature and Nanomedicine

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To Sachie, Paul, and Marie

Preface

With the growth of complex system science and the expansion of nanotechnology, there is increased need to distinguish between two related mechanisms, "self-organization" and "self-assembly," occurring in physical and biological systems. Basically, as pointed out in a recent issue of the journal *Complexity*, self-organization is a nonequilibrium process; in contrast, self-assembly leads toward equilibrium. Nevertheless, self-organization and self-assembly are regularly used interchangeably, as both explain how collective order is developed from dynamic small-scale interactions [J.D. Halley, D.A. Winkler, Consistent concepts of self-organization and self-assembly, *Complexity* 14 (2008) 10–17]. Hence, in this book, all use of the term "self-assembly" (which some chemists classify as either static or dynamic [*Science* 295 (2002) 2418–2421]) is here only intended within a "dynamic" sense; specifically, "dynamic" self-assembly corresponds to what biologists understand as self-organization [*Complexity* 14 (2008) 10–17].

Stable gas nanoemulsions, existing in natural waters, represent self-assembled coated microbubbles (also known as "gas-in-liquid emulsions"). Similarly, in certain artificial media (namely, lipid dispersions modeled from natural microbubbles), stable nanoemulsions are also able to self-assemble (self-organize) readily. (Consequently, the first (1986) and expanded second (2003) editions of a related earlier book were entitled *Stable Gas-in-Liquid Emulsions* (with the subtitle *Production in Natural Waters and Artificial Media*). Yet, this much-expanded current book, that is, 12 chapters longer than the 2003 monograph, is more inclusive in its scope and accordingly entitled *Stable Nanoemulsions*.) In this specific case, the nanoemulsions comprise both "lipid-coated microbubbles (LCM)" (i.e., the gas-emulsion subpopulation) and "related lipid nanoparticles" (i.e., a particle-like subpopulation including mostly colloidal liquid crystals). Various measurements and other published findings indicate that the LCM's structural characteristics help drive and govern a continual and reversible (molecular and/or supramolecular) lipid interchange, with the nanoparticle subpopulation, in these self-assembling lipid nanoemulsions.

The term "LCM" is utilized, in this multidisciplinary book, to accurately trace the chronological development (and functional conversion) of the "LCM/nanoparticle-derived" colloidal system: (1) from its (modeling after natural microbubble surfactant and) early biomedical application as an imaging agent (in Chapters 1–12, which focus mainly on the less numerous micron-scale colloidal species) into (2) the later adaptation of exactly the same mixed-lipid (e.g., Filmix®) colloidal system (in Chapters 13–27, which

focus more upon the vastly more numerous nanoscale colloidal species) for nanomedical application as a (LCM/nanoparticle-derived) drug-delivery vehicle. In addition, as explained in the chapters, newer models of several selected particle-size-analysis instruments have revealed that approximately 90% of these LCM/nanoparticle-derived colloidal species are actually smaller than 200 nm in diameter, while over 99% of the same mixed-lipid colloidal species (detectable via optical-particle-counter data) are documented to be smaller than 300 nm in diameter.

In this book, much experimental data are reviewed in detail and updated, along with the relevant current literature, which collectively demonstrate that this type of stable lipid nanoemulsion (upon intravenous injection) is capable of "active targeting" to tumors, and to certain lesion sites, via the process of receptor-mediated endocytosis. Hence, this LCM/nanoparticle-derived lipid formulation has been used successfully, in animals, as a drug-delivery agent that actively targets antineoplastic drug (e.g., paclitaxel) against tumor cells that commonly overexpress certain surface receptors, which fall within the category known as "lipoprotein receptors." Moreover, this LCM/nanoparticle-derived lipid nanoemulsion contains no phospholipids, proteins, peptides, and carbohydrates, and no chemical modification of the drug (paclitaxel) is required. Hence, this category of parenteral lipid nanoemulsion avoids various past problems reported for earlier versions of (actively) targeted drug-delivery agents utilizing such lipoprotein-receptor-mediated endocytic pathway(s). (Consequently, a human clinical trial is now in preparation, by a pharmaceutical company, for targeted drug delivery of paclitaxel to tumors in patients using an LCM/nanoparticle-derived drug-delivery agent.) In addition, as detailed in later chapters of the book, there are several noncancerous lesion/injury sites involving certain proliferative processes (e.g., atherosclerosis) which include overexpression of cell-surface lipoprotein receptors. Therefore, the scope of potential clinical trials, which are applicable to the pharmaceutical category referred to as LCM/nanoparticle-derived lipid nanoemulsions, can now include the targeted chemotherapy of hyperproliferative diseases, for example, atherosclerosis and CNS-injury sites. In these last few chapters, several sections detail how one particular lipid-nanoemulsion agent (Filmix®) in this pharmaceutical (LCM-related) category, as well as a few other closely related protein-free parenteral lipid nanoemulsions, accordingly exhibit much (literature-supported) potential for providing "actively targeted" chemotherapy of atherosclerotic lesions in human subjects. (Such targeted chemotherapy is also in harmony with goals of the current U.S. National Nanotechnology Initiative, which include nanomedical approaches to drug delivery that focus on developing nanoscale particles (or macromolecules) to improve drug bioavailability, that is, often using targeted nanoparticles for delivering drugs with cell precision and less side effects.)

The book has been organized into six parts. Parts I and II (Chapters 1–8) describe coated microbubbles in the biosphere, as well as various biochemical, geochemical, surface, and structural properties of natural microbubble

surfactant. Next, artificial LCM and related lipid nanoparticles are described in Part III (Chapters 9–11), while their utilization in biomedical studies with animals is examined in detail in Part IV (Chapters 12–15).

Parts V and VI consist of completely new chapters (i.e., Chapters 16–27) that contribute to a strong nanomedicine focus. These 12 chapters further analyze and characterize this type of self-assembling mixed-lipid nanoemulsion, regarding LCM and especially its predominant mixed-lipid nanoparticle subpopulation. In addition, recent clinical studies with related parenteral (lipid) nanoemulsions are described; this limited clinical review provides added understanding of the development path leading to the human clinical trials—evaluating these parenteral lipid nanoemulsions as new, (actively) targeted, drug-delivery agents. Finally, throughout Parts V and VI, extensive cross-references to the earlier chapters are provided in the text. Furthermore, over 500 new literature references have been added by Parts V and VI, many of which are very recent.

The underlying chemical and biomedical principles covered in each chapter are presented in sufficient detail for this book to be useful to all interested readers worldwide with a working knowledge of chemistry, physics, and biology. Accordingly, the level of readership is intended to include graduate students, researchers, and professional people from widely varying fields. Furthermore, due to the many current and potential applications of stable lipid nanoemulsions, the appropriate readership of this book is likely to be found in industry, universities, government laboratories, and clinical facilities alike.

Thanks are due to the following colleagues for their collaboration on some of the original investigations described in this book and/or their generous help with various experimental measurements: Elisa Barbarese, William Barker, J. Howard Bradbury, Kai-Fei Chang, Stephanie A. Ching, Michael A. Davis, John F. Dunne, Donald C. Grant, Richard J. Guillory, Brendon C. Hammer, Shih-Yieh Ho, Toyoko Imae, Jacob N. Israelachvili, Inam U. Kureshi, Kathleen M. Nellis, Barry W. Ninham, Noboru Oishi, Richard M. Pashley, Neil S. Reimer, P. Scott Rice, Cesareo Saiz-Jimenez, Richard H. Simon, Kent Smith, Candra Smith-Slatas, Charles S. Springer, Ourai Sutiwatananiti, and Linda Vaught. Finally other acknowledgments, in addition to those appearing in the chapters, include permission for using quoted material appearing on p. 15, Copyright© 1981 by the AAAS; p. 26, Copyright© 1972 by the ASME; pp. 9, 12, 18, and 98, Copyright© 1975, 1978, 1978, and 1974, respectively, by the Pergamon Press, Ltd.; p. 271, Copyright© 1973 by Springer-Verlag; pp. 271–272, Copyright© 1993 by the American Chemical Society; and the reprinting of Figure 12.1 on p. 216, Copyright© 1991 by Sage Publications, Inc.

Joseph S. D'Arrigo

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