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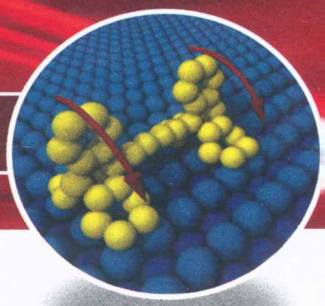
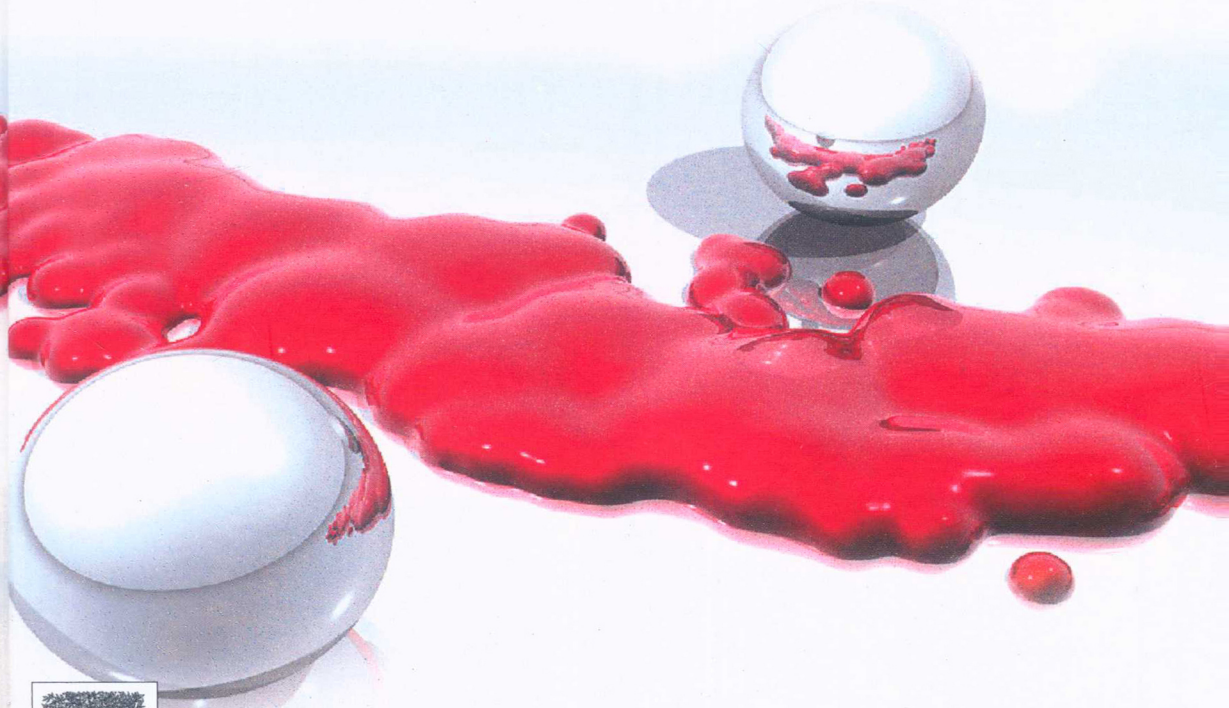


Stable Nanoemulsions
Self-Assembly in Nature and Nanomedicine

稳定纳米乳液
在自然界和纳米医药中的自组装

Joseph D'Arrigo



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导　读

纳米科学与技术自诞生以来，就迅速崛起成为当今世界上科学家广泛研究的高科技领域。本书涉及的药物释放领域是一个交叉学科，未来的成功需要化学、生物学、药学和临床医学等多学科的综合研究。

实际上，正如本书主编 Joseph D'Arrigo 教授所谈到稳定纳米乳液的生成过程中，有必要了解物理与生物系统中“自组装”和“自组织”之间共同点与区别。存在于天然水中的稳定气相乳液是自组装涂层微泡。而在特定人工介质中（模仿天然微泡的脂质分散相），稳定纳米微乳液也能够很容易实现自组装（自组织）。此外，油脂涂层微气泡 LCM 的结构特征有助于驱动和控制在这些自组装油脂纳米乳液体系中持续可逆的油脂分子或超分子与纳米粒子团聚体之间相互交换。因此，《稳定纳米乳液》这本书正是在这种情况下及时出版的，它对稳定微泡乳液的种类、制备、表征及其在药物缓释领域的应用进行了系统的阐述和总结，为当前肿瘤等人类流行病化疗方法和应用指明了方向。

本书着重阐述了利用“LCM”结构特征能够准确跟踪“LCM/派生一纳米粒子”胶体系统的时间进程和功能转换：（1）从表面活性剂的自然微泡早期作为显影剂用于生物医学开始（第 1～12 章涉及少量的微米尺寸的胶体体系）到（2）后来混合油脂分子（如 Filmix®）胶体体系（第 13～27 章着重于阐述大量纳米尺寸胶体体系）作为一种 LCM/派生纳米粒子药物缓释胶囊用于生物医药领域。

通过阅读本书的目录，读者可以发现各章节间的内在联系。本书包括 27 章，分为六部分：

第Ⅰ和Ⅱ部分（1～8 章）描述了包覆微泡的生物球和不同天然微泡表面活性剂的生物化学、胶体化学、表面及结构性能。其中，第 1 章主要讲述了天然水中存在的低浓度气液乳液稳定的重要性及其测试方法。第 2～4 章分别针对水溶性碳水化合物凝胶、水相土壤提取物与天然微泡表面活性剂的特征糖肽类分数进行论述，着重介绍了琼脂糖凝胶方法模拟气泡形成的进展，并讨论了水溶性碳水化合物凝胶与水相土壤提取物的相同点与不同点，最后着重介绍了天然微泡表面活性剂的特征糖肽类分数的分析方法及生物化学研究结果。第 5 章针对天然微泡表面活性剂的生态化学性能研究给出详细的论述；而第 6 章通过改进朗格缪尔方

法、表面压力－面积（$\Pi-A$）曲线的研究讨论了微泡表面活性剂单分子层的表面性能；进而第7章给出了稳定天然微泡的表面活性剂主导成分的结构；基于上述研究，第8章提出了生理学流体中稳定微泡的竞争假说。

第Ⅲ部分（9～11章）涉及了人工LCM和相关油脂分子纳米粒子的物理性能。其中，第9章通过激光光散射测试得到微泡合成数量及悬浮和持久性与时间关系；第10章通过光子相关谱分析微泡形成、融合、分裂和消失等过程及其尺寸分布、气体可溶性能；最后，第11章给出了人工介质中浓气液乳液的微泡稳定的分子机理，包括微泡寿命和内部聚集相互作用，单分子层的分子堆积及曲率等。

第Ⅳ部分（12～15章）针对油脂包覆微泡及相关油脂纳米粒子讨论了对其在动物体的生物医药领域研究情况。其中，第12章主要介绍了油脂包覆微泡用于瘤的目标成像和针对性空化医疗等领域；第13章着重于LCM用于肿瘤的靶向药物缓释治疗的介绍；最后，第14章和第15章分别介绍了瘤细胞选择性吞噬LCM的可能机理和肿瘤细胞的吞噬行为与LCM粒径的关系。

第Ⅴ和Ⅵ部分（16～27章）着重于临床应用的纳米医药领域。第Ⅴ部分进一步分析和表征了该类型的自组装混合油脂分子纳米乳液，如LCM及主流的混合油脂分子纳米粒子体系（第16章），LCM组成与纳米粒子亚群的主要相互作用（第17章），形成“LCM/派生纳米粒子”（第19章）选择肠外油脂纳米乳液（第20章）的临床进展。此外，第Ⅵ部分着重于“LCM/派生纳米粒子”纳米乳液生物脂基因多态性（第22章）和药物受体吞噬性（第23～24章）及其临床领域（第25～26章）的研究；最后，第27章给出靶向油脂纳米乳液的未来研究方向。

本书是由Joseph D'Arrigo博士主编。主要研究领域涉及LCM体系技术在医疗（治疗和诊断）的应用。Joseph D'Arrigo教授于1967年毕业于美国纽约州立大学Queens学院，并于1972年在美国加州大学洛杉矶分校脑研究所（Brain Research Institue）获得神经科学专业博士学位。他分别在美国犹他州立大学医学院（1972—1973年）、犹他州立大学盐湖城分校（1973—1975年）、夏威夷大学医学院（1975—1984年）从事博士后研究或工作。此后，全职担任CAV-CON公司的研发总监及首席执行官。目前，他已经发表37篇论文，出版3本专业书籍，申请获得9项专利。

此外，本书注重基础和前沿的结合，强调科研与实践，各章节都基本遵循由

浅入深的写作思路，先从基本理论或概念出发，循序渐进地过渡到学科的前沿进展。因此，本书受众是广泛的。对于初涉化学和生物医药的读者而言，有助于了解稳定油脂分子纳米乳液当前和潜在应用。读者的范围倾向于不同领域的研究生、研究人员和职业人员，特别适用于具有化学、物理和生物知识的对纳米乳液感兴趣的读者。通过阅读该书可以准确把握相关领域的研究热点，发现重要的问题。相信读者会从本书中得到帮助和启示。

赵永彬

北京低碳清洁能源研究所

序　言

随着复杂系统科学的发展和纳米技术的进步，有必要在物理与生物系统中了解“自组装”与“自组织”二者的区别。*Complexity* 最近一期指出，“自组织”是非平衡过程而“自组装”倾向于平衡过程。此外，由于自组装和自组织都是用来解释如何从动态小规模相互作用发展为集体秩序过程而经常被互换使用［J. D. Halley, D. A. Winkler, Consistent concepts of self-organization and self-assembly, *Complexity* 14 (2008) 10-17］。因此，本书中所有涉及的“自组装”概念（它被一些化学家分为动态或静态［*Science* 295 (2002) 2418-2421］）仅仅倾向于“动态”的意思；具体的“动态”自组装被生物学家理解为“自组织”［*Complexity* 14 (2008) 10-17］。

存在于天然水中的稳定气相乳液是自组装涂层微泡（即气液乳液）。与此相似，在某种人工介质中（即模仿天然微泡的脂质分散相），稳定纳米微乳液也能够很容易实现自组装（自组织）（所以，早期相关此领域出版书名为“稳定气液乳液”及副标题为“天然水和人工介质中产物”（第一版（1986）及第二版（2003）。但是，近期出版书籍（12章长于2003年版专刊）涉及了更多领域，因此书名为“稳定微乳液”）。在此特定情况下，纳米乳液不仅包含“油脂涂层微气泡（LCM）”（即气乳液团聚体），还包括“相关油脂纳米粒子”（即包括大多胶体液晶的粒子状团聚体）。不同测试及其他出版的文献证明LCM的结构特征有助于驱动和控制在这些自组装油脂纳米乳液体系中持续可逆的油脂分子或超分子与纳米粒子团聚体之间相互交换。

多学科书籍中利用“LCM”概念能够准确跟踪“LCM/派生一纳米粒子”胶体系统的时间进程（和功能转换）：（1）从它（建模后自然微泡表面活性剂）早期的生物医学应用作为显像剂（1～12章着重论述了少量的微米尺寸的胶体体系）到（2）后来完全相同混合油脂分子（e.g.，Filmix®）胶体体系（13～27章集中大量纳米尺寸胶体体系）在纳米医药应用作为一种（LCM/派生纳米粒子）药物缓释胶囊。此外，上述章节涉及的几种被选择粒子尺寸分析设备的最新模型揭示了几乎90%的LCM/派生一纳米粒子胶体系统的直径小于200nm，而99%以上的相同混合油脂分子胶体体系（通过光学粒子计数器检测到数据）的直径小于300nm。

随着当前相关文献的更新，本书中更多的实验数据证明这种稳定油脂分子纳

米乳液（静脉注射后）通过受体介导内吞作用能够“主动靶向”到瘤或某种病灶部位。因此，由于癌细胞通常具有某种过量表面受体（属于“脂蛋白受体”），这种 LCM/派生一纳米粒子油脂配方已经作为治疗癌细胞的药物缓释剂（即主动靶向抗肿瘤药物）被成功用于动物，而且“LCM/派生一纳米粒子”油脂分子纳米乳液不包含磷脂、蛋白质、肽、碳水化合物及不需要对药物（paclitaxel）做任何化学改性。因此，该类肠外油脂分子纳米乳液避免了通过脂蛋白受体介导内吞途径的（活性）靶向药物缓释剂的过去报道的问题（因此，某个制药公司正在准备使用 LCM/派生一纳米粒子药物缓释剂用于靶向药物缓释治疗癌变病人的人类临床试验）。此外，本书随后章节详细描述了涉及某种增殖过程（e. g. 动脉粥样硬化）的多种非癌性病变/损伤部位主要包括过量的细胞表面脂蛋白受体。因此，应用制药类的“LCM/派生一纳米粒子”油脂分子纳米乳液到人类临床试验的潜在范围主要包括过度增生性疾病的靶向化疗，如动脉粥状硬化和 CNS 损伤部位。最后几章不仅仅介绍一种特殊油脂分子纳米乳液试剂（Filmix®）用于制药领域还涉及了一些其他相关的无蛋白质肠外油脂分子纳米乳液及其通过“活性靶向”化疗治愈人类身体上动脉硬化病变的潜在应用（这种靶向化疗也是当前美国国家纳米科技倡议的目标，包括纳米医药途径用于药物缓释，集中于发展纳米尺寸离子（或大分子）改善药物生物有效性，即使用靶向纳米粒子传输药物到细胞的精确度和较少副作用）。

本书分为六部分，第Ⅰ和Ⅱ部分（1～8 章）描述了包覆微泡的生物球和不同天然微泡表面活性剂的生物化学、胶体化学、表面及结构性能。此后，第Ⅲ部分涉及了人工 LCM 和相关油脂分子纳米粒子（9～11 章），而第Ⅳ部分（12～15 章）对其在动物体中的生物医药领域研究给出了详细解释。

第Ⅴ和Ⅵ部分（16～27 章）着重于纳米医药领域。其中进一步分析和表征了这类型的自组装混合油脂分子纳米乳液，如 LCM 及主流的混合油脂分子纳米粒子体系。此外，也涉及了相关肠外（油脂分子）纳米乳液在临床上的研究；仅有临床研究进一步增加了人类临床实验的发展的了解一评估了这些肠外油脂分子纳米乳液作为新的、（活性）靶向、药物缓释试剂。最后，贯穿第Ⅴ和Ⅵ部分中广泛交叉引用了前面章节涉及的文献。进而，涉及了 500 篇以上的最近的文献。

本书中各个章节涉及的相关化学和生物医药原理有助于具有化学、物理和生物知识的世界范围内感兴趣的读者学习。因此，读者的范围倾向于不同领域的研究生、研究人员和职业人员，而且由于稳定油脂分子纳米乳液当前和潜在应用，本书也适用于工业、大学、政府研究室和临床公司等。

非常感谢下面相关人员在本书中的贡献：Elisa Barbarese，William Barber，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, ToyokoImae, Jacob N. Israelachvili, Inam U. Kureshi, Kathleen M. Nellis, Barry W. Ninham, Noboru Oishi, Richard H. Simon, Kent Smith, Candra Smith-Slatas, Charless S. Springer, OuraiSutiwatananiti, and Linda Vaught. 最后，还要感谢其他相关各章中出现的贡献者，包括 P. 15 出现材料的许可，copyright© 1981 by AAAS; P. 26, copyright© 1972 by ASME; pp. 9, 12, 18 and 98, copyright© 1975, 1978, 1978, and 1975, respectively, by the Pergamon press, Ltd.; p. 271, copyright© 1981 by Springer-verlag; pp. 271-272, copyright© 1981 by the American chemical society; and reprinting of Figure 12.1 on p. 216, copyright© 1991 by Sage Publications, Inc.

Joseph S. D'Arrigo

（赵永彬　译）

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.

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Joseph S. D'Arrigo

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