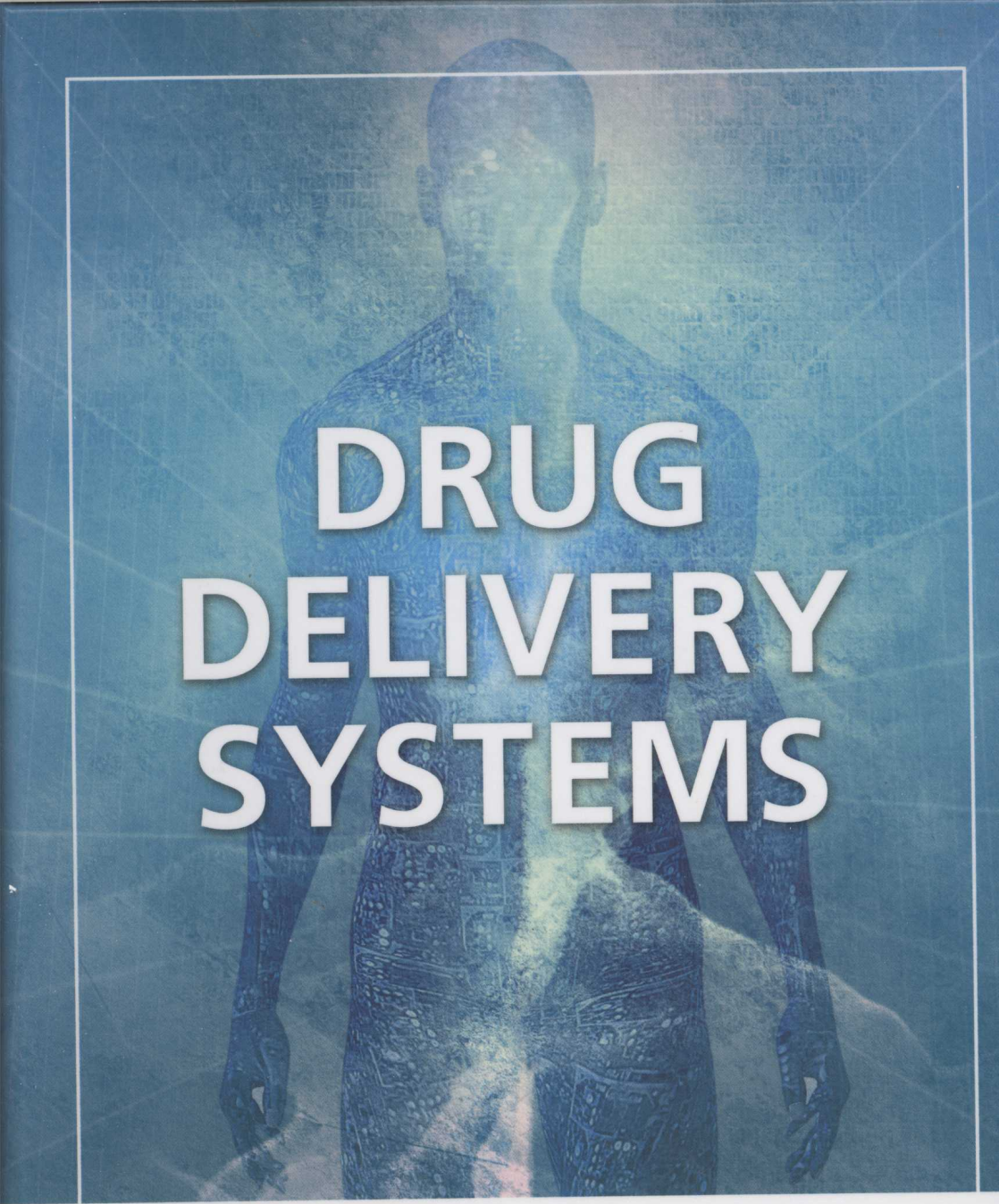

# DRUG DELIVERY SYSTEMS

Third Edition

Vasant V. Ranade
John B. Cannon

CRC Press
Taylor & Francis Group

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# Preface to the Third Edition

A few years ago, Dr. Mannfred Hollinger passed away unexpectedly. He will be missed and remembered by his colleagues for his expertise in the pharmacological and toxicological sciences and, in particular, drug delivery.

During the preparation of the third edition of this book, I was fortunate to receive timely help form Dr. John Cannon, who agreed to offer his views and comments on various forms of drug delivery systems, especially oral, transdermal, transmucosal, and liposomal forms of drug delivery. In this edition, we have attempted to include relevant information regarding drug delivery systems that was published through the end of 2009. A new chapter on nanoscience and nanotechnology for drug delivery has been included. In a short, concise volume on drug delivery such as this one, it is almost impossible to include every detail on the subject. However, we have made an honest attempt to include research and development work so that the reader will be adequately informed about the current trend and the future prospects of the science of drug delivery.

We would like to thank our colleagues, especially Dr. John Somberg and Ms. Susan Somberg, for their continued support. We would also like to express our deep sense of gratitude to our wives, Usha and Charlene, for their constant encouragement and assistance. Also we would like to thank staff of CRC Press/Taylor & Francis Group for their patience, understanding and help during preparation of this book.

Finally, as an interesting note, Dr. Stephen R. Covey in his bestseller book, *The 7 Habits of Highly Effective People*, mentioned that "I did not invent them and take no credit for them. I have simply identified and organized them into a sequential framework." This scenario is also applicable to our endeavor of presentation of the science of drug delivery in this edition.

# Authors

**Vinayak (Vasant) V. Ranade**, PhD, is director of chemical sciences for Academic Pharmaceuticals Inc. in Lake Bluff, Illinois. He also holds a faculty position in the Department of Pharmacology at Rush University Medical Center in Chicago, Illinois.

Dr. Ranade received his PhD in organic chemistry from Bombay University in 1965 and his postdoctoral training in the College of Pharmacy at the University of Michigan, Ann Arbor, Michigan. He has worked as a research chemist for Abbott Laboratories, Mallinckrodt Inc., and DuPont Critical Care. Dr. Ranade is a member of the American Chemical Society; APhA Academy of Pharmaceutical Sciences; and the honorary society, Sigma Xi. He was awarded the Council of Scientific and Industrial Research Fellowship and was elected fellow of the American Institute of Chemists. He was the corecipient of the Genia Czerniak Prize for Nuclear Medicine and Radiopharmacology.

Over the past 40 years, Dr. Ranade has been a reviewer for a number of scientific journals and has presented research work at the American Chemical Society, the APhA Academy of Pharmaceutical Sciences, and the American College of Cardiology and Pharmacology meetings. He has published more than 200 papers, including original and review articles, book chapters, book reviews, and abstracts for presentation. He is the recipient of several U.S. patents and his research work has also been included in Canadian, European, and International patents. He coauthored the first and second editions of the book titled *Drug Delivery Systems* published by CRC Press. He also developed and directed courses on drug delivery technologies for the Center of Business Intelligence (Massachusetts) and the Center for Professional Advancement (New Jersey) for presentation in Europe and the United States. Dr. Ranade is on the editorial board of the *American Journal of Therapeutics* and his biography is listed in *American Men and Women of Science and Who's Who in Technology Today's* (Chemistry and Biotechnology).

Dr. Ranade's significant contributions to pharmaceutical research and development for marketed products include radiosynthesis, formulations, and chiral chromatographic separations. He also worked as a consultant in the areas of chemical and pharmaceutical technology for some industrial organizations, securities market analysis companies, and research organizations in the United States.

**John B. Cannon**, PhD, Trinity International University, Deerfield, Illinois, is currently a visiting assistant professor of chemistry at Trinity International University in Deerfield, Illinois, and is also president of his own drug delivery and pharmaceutics consulting firm, Targeted Drug Solutions, Inc., in Grayslake, Illinois. He received his BS in chemistry from Duke University and his PhD in organic chemistry from Princeton University; his dissertation research focused on organo-transition metal chemistry. After a postdoctoral fellowship at the University of California at San Diego investigating hemoglobin model compounds, Dr. Cannon served in faculty positions at Northern Illinois University and Cleveland State University (Ohio),

as well as in visiting scientist research positions at Scripps Clinic and Research Foundation (California) and at Cornell University Medical College (New York). He made significant contributions to understanding the interaction of metalloporphyrins and heme proteins with biological membranes and liposomes. This was followed by a research chemist position at American Cyanamid Company's Veterinary Research Division investigating parenteral controlled release formulations of protein and peptide hormones. He recently retired from a 20 year career as a pharmaceutical scientist at Abbott Laboratories, where he focused on oral lipid-based drug delivery systems, water-insoluble drug formulations, liposomes, emulsions, topical/transdermal drug delivery, preformulation/basic pharmaceutics, and Phase I formulation development. He is a member of the American Association of Pharmaceutical Scientists, the American Scientific Affiliation, the American Chemical Society, and Sigma Xi. Dr. Cannon has published over 30 papers in peer-reviewed journals, 12 book chapters, and 4 patents. He has also made about 15 presentations with published abstracts at meetings of various scientific societies and has been a reviewer for a number of scientific journals.

# Contents

# 1 Site-Specific Drug Delivery Using Liposomes and Emulsions as Carriers*

## INTRODUCTION

Over the past three decades, significant advances have been made in drug delivery technology. This effort, pioneered by Alza Laboratories of Palo Alto, California,[1,2] among others, has been accelerated in recent years due to a decline in the development of new drug entities. Drug delivery has now become a multidisciplinary science consisting of biopharmaceutics and pharmacokinetics. Great strides have also been made by physical biochemists, pharmacists, and other pharmaceutical research scientists working in university and industrial laboratories.[3–6]

The underlying principle that drug delivery technology, per se, can bring both therapeutic and commercial value to health care products has been widely accepted. Recently, large pharmaceutical companies have been losing their market share to generic competitors with increasing rapidity after their patents expire. This has created an intense need for presenting "old" drugs in new forms and utilizing novel forms of delivery. As a result, companies developing new drug delivery systems seem to enjoy a good return on their investment in the form of increased revenues and market share.[7]

In the United States, the Drug Price Competition and Patent Term Restoration Act (also known as ANDA-Exclusivity Provisions Act) was passed in 1984. This provided new incentives to manufacturers who can distinguish their products from competition, with features such as longer dosage schedules, improved safety profiles, new indications for existing drugs, and new combinations.[8]

The following chapters, which focus on the area of research and development in the drug delivery field, have been divided into five sections:

1. Site-specific drug delivery
2. Polymers and implantable drug delivery systems
3. Oral drug delivery
4. Transdermal, transmucosal, ocular, and miscellaneous drug delivery systems
5. Regulatory considerations and global outlook

* Adapted in part from Ranade, V.V., *Drug delivery systems.* 1. Site specific drug delivery using liposomes as carriers, *J. Clin. Pharmacol.*, 29, 685, 1989. With permission of the *J. Clin. Pharmacol.*, and J.B. Lippincott Publishing Company, Philadelphia, PA.

Drug delivery, which takes into consideration the carrier, the route, and the target, has evolved into a strategy of processes or devices designed to enhance the efficacy of therapeutic agents through controlled release. This may involve enhanced bioavailability, improved therapeutic index, or improved patient acceptance or compliance. Drug delivery, or controlled release, has been defined by Flynn as "the use of whatever means possible, be it chemical, physiochemical, or mechanical, to regulate a drug's access rate to the body's central compartment or, in some cases, directly to the involved tissues."[9]

Tomlinson[10] has emphasized features such as exclusive delivery to specific components, access to primarily inaccessible sites, protection of body from unwanted deposition, controlled rate and modality of delivery to pharmacological receptors, and reduction in the amount of active principal employed. Tomlinson[10,11] has also described the properties that are needed for site-specific carriers, as well as properties that are biological, drug related, and carrier related.

## LIPOSOMES IN DRUG DELIVERY

### Regional Drug Delivery

Most efforts to make drug therapy more efficient by direct delivery of drugs to affected tissues have focused on local or regional injection techniques, such as intra-arterial or infusions into body cavities, such as the peritoneum. The benefits of regional therapy include reducing systemic toxicity and achieving peak drug levels directly at the target site. However, these methods of administration have met with limited success. For example, although intra-arterial injections effectively concentrate drugs at certain tumor sites, in others the drug is cleared from the system so rapidly that the benefits are not realized. Currently, pharmaceutical researchers are trying to design drug delivery systems that will localize drugs and affect only the afflicted tissues. A carrier system that has received considerable attention in this regard is liposomes.[12–17] Emulsions have received somewhat less attention as carriers of therapeutic agents, but they also have the potential for delivery of water-insoluble drugs, which will be discussed later.

Liposomes consist of a bilayer of amphipathic lipid molecules (usually phospholipids) encapsulating an aqueous space.[18] The lipid molecules arrange themselves into layers, referred to as lamellae, by exposing their polar "head" groups toward the water phase. The hydrophobic hydrocarbon "tail" groups adhere together in the bilayer, thus forming close, concentric, bimolecular lipid leaflets separating aqueous compartments. Liposomes vary in charge and size, ranging from 20 nm to 10 μm, depending on the method of preparation and the lipids used.

Drug molecules can be either encapsulated in the aqueous space or intercalated into the bilayer (see Figures 1.1 and 1.2).[265] The exact location of the drug in the liposome depends upon the physiochemical characteristics of the drug and the composition of the constituent lipids.[19] Stable liposomes from phospholipids are formed only at temperatures above the "gel to liquid-crystalline" phase transition temperature ($T_c$). This represents the melting point of the acyl chains. All phospholipids have a characteristic $T_c$, which depends upon the nature of the polar head group and on the length and degree of unsaturation of the acyl chains.[19,20] Above the transition temperature, phospholipids form a liquid-crystalline phase that constitutes increased

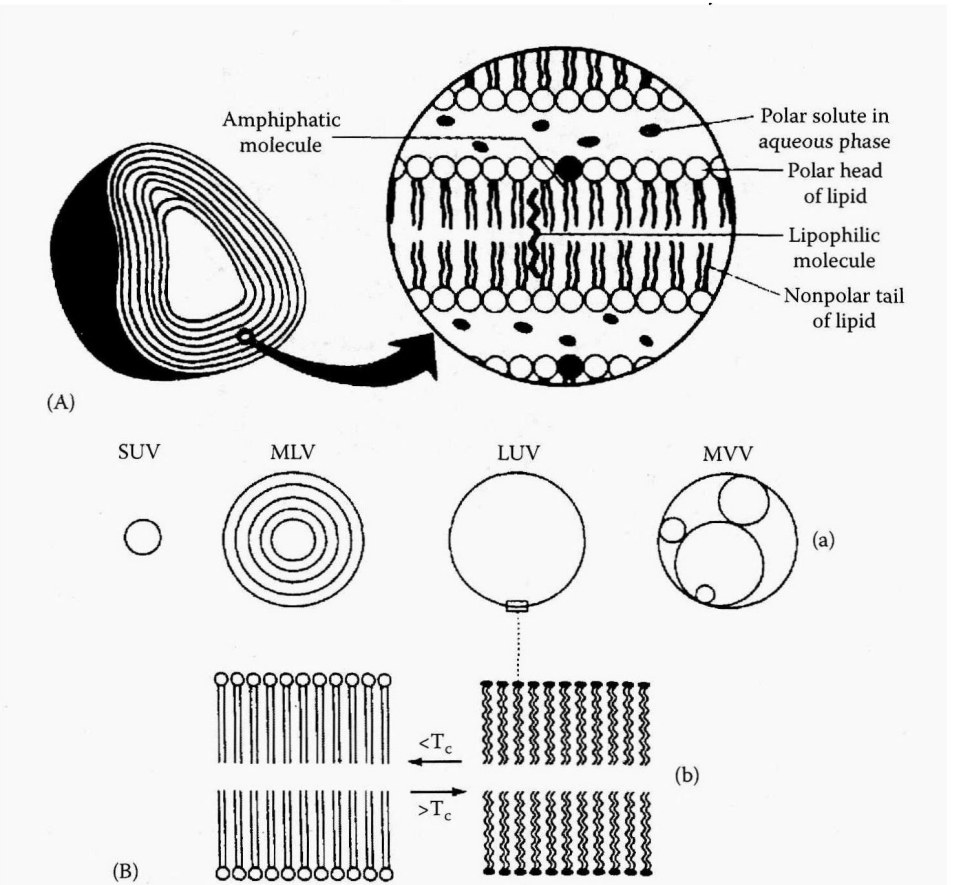


**FIGURE 1.1** Schematic of a bilayer vesicle or liposome. (A) Multilamellar liposome showing interaction with drugs. (Weiner, A.L., Cannon, J.B., and Tyle, P.: Commercial Approaches to the delivery of Macrmolecular drugs with liposomes, in Rossoff, M., Ed., *Controlled Release of Drugs: Polymers and Aggregate Systems*, p. 225, 1989. Copyright Wiley-VCH GmbH & Co, KGaA. Reproduced with permission.) (B) Schematic showing (a) differences between SUV, MLV, LUV, and MVV; and (b) gel to liquid crystalline phase transition of a lipid bilayer at the transition temperature, $T_c$. (From Kadir, F. et al., In *Injectable Drug Development*, Gupta, P.K. and Brazeau, G.A., Eds., Interpharm Press, Englewood, CO, 1999, p. 339. With permission.)

mobility of the acyl chains. A reduction in temperature below the $T_c$ creates a transition to a more rigid gel state. This results in restrained mobility of the tightly packed acyl chains. When the liquid molecules arrange themselves to form closed bilayer structures containing water and solutes, drugs are trapped between the adjacent planes of the polar head groups. This compartmentalization has been discussed in detail by Roerdink et al.[14]

## Chemical Characteristics of Liposomes

Liposomal affinity for various tissues can be modified by synthesizing liposomes containing phospholipids with various fatty-acid chain configurations. These substances

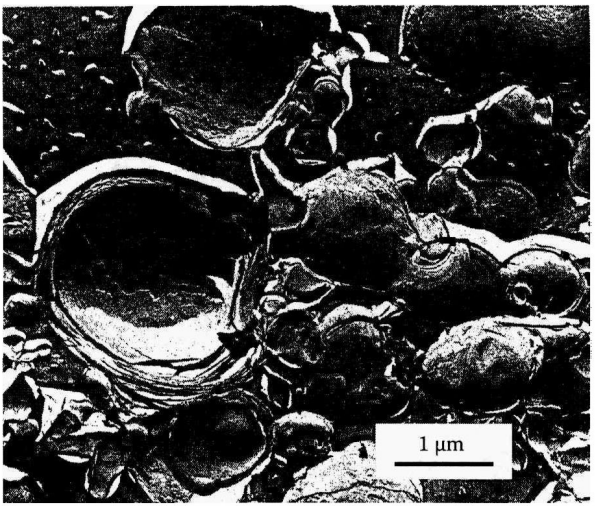


**FIGURE 1.2** Micrograph view of a liposome. (Weiner, A.L., Cannon, J.B., and Tyle, P.: Commercial Approaches to the delivery of Macrmolecular drugs with liposomes, in Rossoff, M., Ed., *Controlled Release of Drugs: Polymers and Aggregate Systems*, p. 225, 1989. Copyright Wiley-VCH GmbH & Co, KGaA. Reproduced with permission.)

may have either solid, gel, fluid, or liquid crystalline character dependent on temperature and conditions.[21,22] Also, altering the charge on the liposome vesicle can greatly influence its distribution in the body. Negatively charged vesicles, for example, can enter the cell by fusion, allowing the drug to be discharged into the cell cytoplasm. Neutral vesicles, on the other hand, are more likely to be incorporated into the cell by phagocytosis, exposing the drug to the lysosomal hydrolytic system of the cells. Positive- and neutral-liposomal vesicles are cleared more slowly than negatively charged ones.

A variety of phospholipids can be used to prepare liposomes. The lipid most widely used is phosphatidylcholine (PC),[23,24] which has been used individually or in combination with cholesterol. Cholesterol is known to condense the packing of phospholipids in bilayers above the $T_c$ and modulates the fluidity of the bilayer. Cholesterol also reduces the permeability of the bilayers to encapsulated compounds. Structures of these lipids are shown in Figure 1.3.

Negatively charged lipids such as phosphatidic acid, phosphatidylglycerol (PS) are usually used in order to provide a surface charge to the liposomes. For drug molecules encapsulated in the aqueous space, the bilayer serves as a diffusion barrier, permitting the liposomes to serve as a rate-controlling input device. Papahadjopoulos and coworkers have done pioneering research in trying to establish and develop the liposomal delivery system from experimental therapeutics to clinical applications.[25–29] The introduction of this delivery system directly to the target site (such as the eye, lung, or bladder) is a well-established approach for treating local diseases, and liposomes have been shown to play a beneficial role when applied in this way. Positively charged lipids such as stearylamine (STA) can also be used to provide a charge to the lipid bilayer, but these are generally more toxic than negatively charged lipids.