

DRUG DELIVERY SYSTEMS

T h i r d E d i t i o n

**Vasant V. Ranade
John B. Cannon**

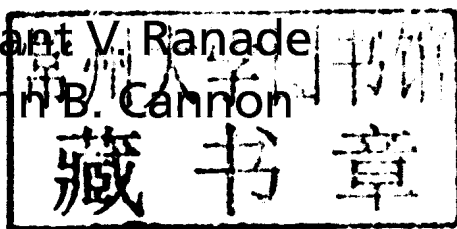


CRC Press
Taylor & Francis Group

DRUG DELIVERY SYSTEMS

T h i r d E d i t i o n

Vasant V. Ranade
John B. Cannon



CRC Press

Taylor & Francis Group

Boca Raton London New York

CRC Press is an imprint of the
Taylor & Francis Group, an **Informa** business

CRC Press
Taylor & Francis Group
6000 Broken Sound Parkway NW, Suite 300
Boca Raton, FL 33487-2742

© 2011 by Taylor and Francis Group, LLC
CRC Press is an imprint of Taylor & Francis Group, an Informa business

No claim to original U.S. Government works

Printed in the United States of America on acid-free paper
10 9 8 7 6 5 4 3 2 1

International Standard Book Number: 978-1-4398-0618-0 (Hardback)

This book contains information obtained from authentic and highly regarded sources. Reasonable efforts have been made to publish reliable data and information, but the author and publisher cannot assume responsibility for the validity of all materials or the consequences of their use. The authors and publishers have attempted to trace the copyright holders of all material reproduced in this publication and apologize to copyright holders if permission to publish in this form has not been obtained. If any copyright material has not been acknowledged please write and let us know so we may rectify in any future reprint.

Except as permitted under U.S. Copyright Law, no part of this book may be reprinted, reproduced, transmitted, or utilized in any form by any electronic, mechanical, or other means, now known or hereafter invented, including photocopying, microfilming, and recording, or in any information storage or retrieval system, without written permission from the publishers.

For permission to photocopy or use material electronically from this work, please access www.copyright.com (<http://www.copyright.com/>) or contact the Copyright Clearance Center, Inc. (CCC), 222 Rosewood Drive, Danvers, MA 01923, 978-750-8400. CCC is a not-for-profit organization that provides licenses and registration for a variety of users. For organizations that have been granted a photocopy license by the CCC, a separate system of payment has been arranged.

Trademark Notice: Product or corporate names may be trademarks or registered trademarks, and are used only for identification and explanation without intent to infringe.

Visit the Taylor & Francis Web site at
<http://www.taylorandfrancis.com>

and the CRC Press Web site at
<http://www.crcpress.com>

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 from 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 pharmaceuticals 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 pharmaceuticals, 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

Preface to the Third Edition	xv
Authors.....	xvii

Chapter 1	Site-Specific Drug Delivery Using Liposomes and Emulsions as Carriers	1
	Introduction	1
	Liposomes in Drug Delivery	2
	Regional Drug Delivery	2
	Chemical Characteristics of Liposomes.....	3
	Liposome-Drug Concept.....	5
	Liposome Size	5
	Targeting Ligands.....	6
	Problems and Advantages of Liposomal Drug Delivery.....	6
	Manufacturing Methods and Issues	8
	Liposomes as Carriers of Therapeutic Agents	12
	Application	12
	Liposomal Products and Manufacturers	15
	Parenteral Emulsions.....	18
	Recent Advances and Future Prospects	20
	Highlights of Current Research.....	20
	Concluding Remarks	32
	References	32
Chapter 2	Site-Specific Drug Delivery Utilizing Monoclonal Antibodies	47
	Introduction	47
	Chemistry	47
	Polyclonals vs. Monoclonals.....	47
	Conjugation of Antibodies.....	48
	Production of Monoclonal Antibodies	48
	Continuously Proliferating Cell Lines.....	49
	Human–Human Hybridomas	49
	Large-Scale Production	50
	Drug–Monoclonal Antibody Conjugates for Drug Targeting	50
	Principles	50
	Drug Antibody Bonding.....	51
	In Vitro and In Vivo Testing.....	51
	Recent Studies with Monoclonal Antibodies	54
	Highlights of Current Research.....	54
	Conclusion and Basis for Future Trends.....	70
	References	71

Chapter 3	Role of Polymers in Drug Delivery	79
	Introduction	79
	Currently Available Polymers	79
	Diffusion-Controlled Systems	79
	Solvent-Activated Systems	80
	Chemically Controlled Systems	80
	Magnetically Controlled Systems.....	80
	Soluble Polymers as Drug Carriers.....	81
	Pinocytosis.....	81
	Ideal Soluble Polymers	82
	Biodegradable or Bioerodible Polymers.....	84
	Drug Release by Matrix Solubilization	90
	Erodible Diffusional Systems.....	91
	Monolithic Systems	91
	Mucoadhesive Polymers.....	94
	Polymers Containing Pendant Bioactive Substituents.....	98
	Matrix Systems.....	101
	Heparin-Releasing Polymers.....	103
	Ionic Polymers.....	104
	Oligomers	109
	Miscellaneous.....	109
	Recent Advances	111
	Conclusion	122
	References	124
Chapter 4	Implants in Drug Delivery	137
	Introduction	137
	Insulin Delivery as a Model Implant Pump System	138
	Peristaltic Pumps	141
	Fluorocarbon Propellant-Driven Pumps	143
	Osmotic Pumps.....	144
	Miniosmotic Pumps: Systemic Delivery	146
	Miniosmotic Pumps: Local Delivery	146
	Miniosmotic Pumps: Patterned Delivery	147
	Positive-Displacement Pumps	148
	Controlled-Release Micropump	148
	Other Devices	150
	Implants for Contraception.....	150
	Biodegradable	150
	Nonbiodegradable.....	151
	Delivery of Chemotherapeutic Agents Using Implants.....	152
	Recent Advances in Implants and Related Devices (Excluding Inserts)	154

Future Prospects	161
References	162
Chapter 5 Oral Drug Delivery	169
Controlled-Release Formulations	169
Introduction	169
Features of the GI Tract	171
Targeting of Drugs in the GI Tract	172
Mathematical Models for Controlled-Release Kinetics	173
Design and Fabrication of Oral Delivery Systems	174
Dissolution-Controlled Release	174
Osmotically Controlled Release	176
Diffusion-Controlled Release	179
Chemically Controlled Release	184
Miscellaneous Forms of Controlled Release	184
Survey of Oral Controlled-Release Products	198
Recent Advances	198
Current Development of Oral Drug Delivery Systems	205
Conclusion	209
References	210
Enhancing Oral Bioavailability	215
Introduction	215
Increasing Bioavailability of Water-Insoluble Drugs	216
General Approaches for Water-Insoluble Drugs: Salt Formation, Cosolvents, and Particle Size Reduction	216
Lipid-Based and Micellar Formulations	217
Solid Dispersions and Related Technologies	231
Cyclodextrins and Complexation Techniques	234
Increasing Bioavailability of Proteins, Peptides, and Other Drugs with Absorption Problems	235
Recent Advances and Future Prospects	236
References	238
Chapter 6 Transdermal Drug Delivery	243
Introduction	243
Theoretical Aspects of Transdermal Drug Delivery	245
Structure of Human Skin	245
Mechanisms of Penetration	246
Optimization of Percutaneous Absorption and Effects of Penetration Enhancers	253
Development of the Transdermal Therapeutic System	257
Types of Transdermal Patches	257
Formulation	259

Adhesion	260
Bioactivity and Metabolism.....	261
Polymers in Transdermal Delivery Systems	262
Examples of Transdermal Applications	262
Diseases for Which TDD Is Used	262
Current Transdermal Products and Devices	263
“Minimally Invasive” Technologies	265
Iontophoresis Systems.....	267
Microneedle Systems.....	270
Other Minimally Invasive and Combination Systems.....	272
Other Transdermal Controlled-Release Products and Devices	273
Recent Advances and Future Prospects	274
Conclusion	287
References	288
 Chapter 7 Transmucosal and Ocular Drug Delivery	305
Introduction: Transmucosal and Ocular Drug Delivery	305
Pulmonary Drug Delivery.....	305
Introduction	305
Lung Physiology and Pulmonary Drug Administration	305
Pulmonary Drug Delivery Devices	306
Recent Advances	317
Intranasal Drug Delivery	322
Introduction	322
Nasal Physiology and Intranasal Drug Administration.....	323
Nasal Drug Delivery Devices.....	325
Examples of Intranasal Drug Delivery Systems	327
Recent Advances	332
Buccal and Sublingual Drug Delivery	333
Introduction	333
Examples of Buccal and Sublingual Drug Delivery Systems	335
Recent Advances	335
Rectal, Vaginal, and Other Forms of Transmucosal Drug Delivery	337
Intravaginal Delivery.....	337
Rectal Delivery.....	341
Ocular Drug Delivery.....	347
Introduction	347
Relevant Anatomy and Physiology of the Eye.....	348
Examples of Ocular Drug Delivery Systems	352
Recent Advances	357
Conclusions and Future Outlook for Transmucosal and Ocular Drug Delivery.....	359
References	361

Chapter 8	Miscellaneous Forms of Drug Delivery	373
Introduction		373
Pro-Drugs		373
Infusion Devices		382
Pumps		382
Mechanical Pumps		382
Closed- and Open-Loop Systems		382
Programmable and Manual Systems		383
Implantable and External Systems		383
Syringe Pumps		383
Piston Pumps		383
Peristaltic Pumps		383
Balloon Pumps		384
Gas-Pressure Pumps		384
Portable Infusion Pumps		384
Controllers		384
Other External Infusion Systems		385
Percutaneous Catheters		385
Totally Implantable Pump and Reservoir Systems		386
Totally Implantable Portal and Catheter Systems		387
Insulin Delivery		388
Parenteral Prolonged-Action Dosage Forms		391
Complex Formation and Addition of Macromolecules		392
Salts of Low Solubility and Slowly Hydrolyzable Esters		392
Aqueous Suspensions		392
Oleaginous Suspensions and Emulsions		393
Precipitation of Drug in Tissue		393
Implants		393
SC Drug Delivery Systems		394
Intravenous Delivery		395
Magnetically Modulated Systems		397
Intrauterine Delivery		399
Microspheres		403
Hydrogels		406
Microcapsules and Microencapsulation		411
Microparticles—Nanoparticles		414
Colloids and Microemulsions		417
Hollow Fibers		421
Ultrasonically Controlled		422
Liquid-Crystalline Phases		423
Time-Controlled “Explosion Systems”		423
Mammalian Cells		423
Sutures		424
Microsealed Drug Delivery		425

Recent Advances	426
Summary	436
References	436
Chapter 9 Nanoscience and Nanotechnology for Drug Delivery	451
Introduction	451
Nanotechnologies	451
Fundamentals	453
Biopharmaceutical, Physiological, and Clinical	
Considerations	453
Delivery of Small Molecules, Proteins, and Nucleic Acids	463
Nanoethics, Safety, and Risk Assessment	467
Nanomaterial Characterization	467
FDA Regulations and Manufacturers	468
Building Business and Trends	470
Miscellaneous Applications of Nanomaterials	471
Nano-oncology	471
Nanoneurology and Nanoneurosurgery	478
Nanodermatology, Nanopulmonology, Nanogeriatrics,	
Nanoimmunology, and Nanodentistry	479
Nano-orthopedics	480
Nanomicrobiology	480
Nanodevices for Medicine and Surgery	480
Nanocardiology	481
Nano-ophthalmology	481
Nanobiotechnology for Regenerative Medicine and Tissue	
Engineering	482
Nanomolecular Diagnostics	482
Nanotechnology for Gene and Vaccine Delivery	484
Nanoparticles and Nanostructures	485
Nanoparticles	487
Nanocomposites	493
Nanotubes, Nanorods, Nanofibers, and Nanohorns	493
Nanocarriers	499
Nanochips	500
Nanosized Colloids	500
Nanoemulsions	501
Nanocrystals	501
Nanostructures	501
Nanomaterials	502
Nanomedicine and Nanopharmaceuticals	507
Worldwide Development	507
Future Prospects	511
References	513

Chapter 10	Regulatory Considerations for Drug Delivery Systems	525
	Introduction	525
	Current Status of Drug Delivery Technology	528
	Regulatory Requirements	528
	Bioavailability Data	532
	The Reference Standard	533
	Requirements to Demonstrate Drug Controlled-Release	533
	In Vitro Drug Release Data	533
	In Vivo Bioavailability Data	533
	Bioequivalence	540
	Stability Testing	542
	Submission of Documents for Manufacture and Quality	546
	Control of Drug Products	546
	Drug Product (NDAs and ANDAs)	546
	Regulatory Specifications and Methods for Drug Products	548
	Methods of Manufacturing and Packaging	550
	Current FDA Draft Guidelines and Regulations	551
	Implants	555
	Monoclonal Antibodies	556
	Computer Access and Security Requirements	558
	References	559
Chapter 11	Drug Delivery Industry and the Global Outlook	563
	Basis for the Recent Trend	569
	References	572
Index		575

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

Tomlinson¹⁰ 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 μ m, 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

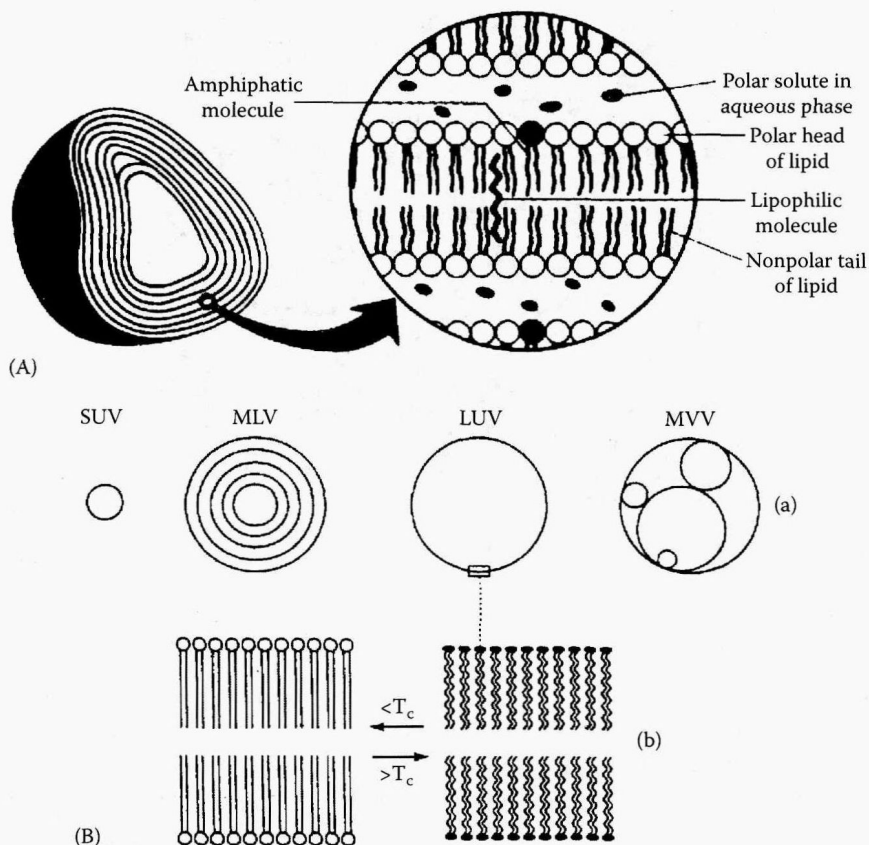


FIGURE 1.1 Schematic of a bilayer vesicle or liposome. (A) Multilamellar liposome showing interaction with drugs. (Weiner, A.L., Cannon, J.B., and Tyle, P.: *Commercial Approaches to the delivery of Macromolecular drugs with liposomes*, in Rossoff, M., Ed., *Controlled Release of Drugs: Polymers and 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

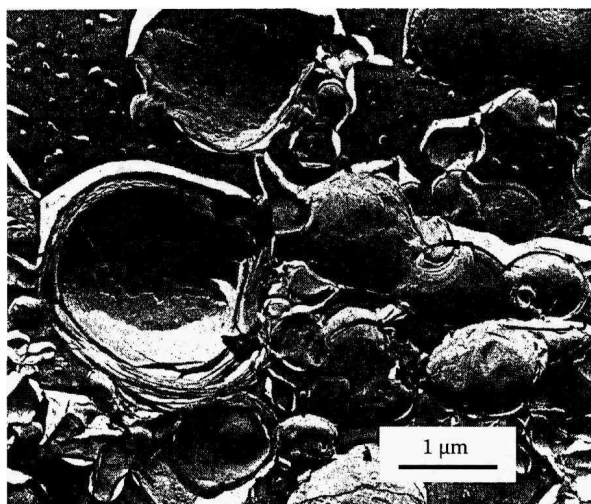


FIGURE 1.2 Micrograph view of a liposome. (Weiner, A.L., Cannon, J.B., and Tyle, P.: Commercial Approaches to the delivery of Macromolecular drugs with liposomes, in Rossoff, M., Ed., *Controlled Release of Drugs: Polymers and Aggregate Systems*, p. 225, 1989. Copyright Wiley-VCH GmbH & Co, KGaA. Reproduced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