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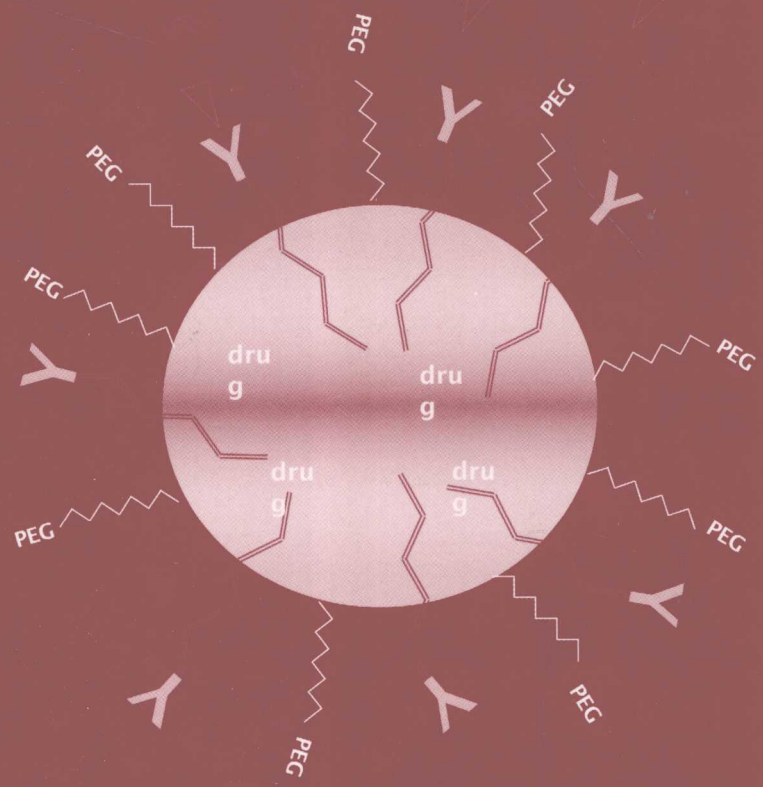
Microencapsulation

Methods and Industrial Applications

Second Edition



edited by
Simon Benita

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Preface to the Second Edition

Prior to writing of the preface for the second edition, I read the preface of the first edition published a decade ago. The assumptions that research, development, and sales of drug delivery systems would intensify in the following years were fully verified and even exceeded expectations. As far as particulate delivery systems are concerned, the research and development has been moving from the micro- to the nano-size scale. There is no doubt that microparticulate controlled delivery systems mainly for topical and oral administration have been successfully exploited by the cosmetic and pharmaceutical industry respectively. However, the pharmaceutical industry is facing an uncertain future in which high clinical development costs coupled with declining drug discovery success rates are decreasing the flow of new products in the R&D pipeline. Experts are now recommending that pharmaceutical companies move from the blockbuster model to a more extensive product portfolio model that focuses on diseases with insufficient therapies mainly in specific populations such as the aging population. Furthermore, investigators are attempting to reformulate and add new indications to existing blockbuster drugs to maintain a reasonable scientific and economic growth rate. I believe that scientists have achieved remarkable successes in the field of oral delivery. There are practical solutions to improving the oral bioavailability of poorly absorbed lipophilic and hydrophobic drugs. Oral controlled microparticulate systems have succeeded in maintaining adequate and effective plasma levels over prolonged periods of time by controlling drug release following oral administration. However, there are still significant unmet medical needs in target diseases such as cancer, autoimmune disorders, macular degeneration and Alzheimer's disease. Most of the active ingredients used to treat these severe diseases can be administered only through the parenteral route. Indeed, molecular complexity associated with drugs and inaccessibility of most pharmacological targets are major constraints and the main reasons behind the increased interest and expanding research on nanodelivery systems, which can carry drugs directly to their site of action. Thus, drug targeting has evolved as the most desirable but elusive goal in the science of drug delivery. Drug targeting offers enormous advantages but is highly challenging and extremely complicated. A better understanding of the physiological barriers a drug needs to overcome should provide the pharmaceutical scientist with the information and tools needed to develop successful designs for drug targeting delivery systems. Optimal pharmacological responses require both spatial placement of the drug molecules and temporal control at the site of action. Many hurdles and drawbacks still need to be overcome through intensive efforts and concentrated interdisciplinary scientific collaboration to reach the desired goals.

The second edition of Microencapsulation, Methods and Industrial Applications comprises 11 expanded and revised chapters and 12 new chapters that reflect the evolution of this discipline in the past decade.

It is my hope that this multi-authored second edition of Microencapsulation, Methods and Industrial Applications will assist and enrich the readers in understanding the diverse types of particulate systems currently available or under development as well as highlight possible applications in the future.

I am deeply grateful to Ms. Madelyn Segev, the secretary of the Pharmaceutics Department of the School of Pharmacy of The Hebrew University of Jerusalem who spared no effort to help me in bringing this project to fruition.

To Einat, Yair and Maytal

Simon Benita

Preface to the First Edition

Research, development, and sales of drug-delivery systems are increasing at a rapid pace throughout the world. This worldwide trend will intensify in the next decade as cuts in public health expenses demand lower costs and higher efficacy. To meet this demand, many efficient drugs currently in use will be reformulated within delivery systems that can be value-added for optimal molecular activity. In addition to the health sector, the cosmetic, agricultural, chemical, and food industries operate in an open marketplace where free and aggressive competition demands novel coating techniques with enhanced effectiveness at the lowest possible cost. Currently, microencapsulation techniques are most widely used in the development and production of improved drug- and food-delivery systems. These techniques frequently result in products containing numerous variably coated particles. The exact number of particles needed to form a single administered dose varies as a function of the final particle size and can lie in either the micro- or nanometer size range for micro- and nanoparticulate delivery systems, respectively.

The microparticulate delivery systems include mainly pellets, microcapsules, microspheres, lipospheres, emulsions, and multiple emulsions. The nanoparticulate delivery systems include mainly lipid or polymeric nanoparticles (nanocapsules and nanospheres), microemulsions, liposomes, and nonionic surfactant vesicles (niosomes).

Generally, the microparticulate delivery systems are intended for oral and topical use. Different types of coated particles can be obtained depending on the coating process used. The particles can be embedded within a polymeric or proteinic matrix network in either a solid aggregated state or a molecular dispersion, resulting in the formulation of microspheres. Alternatively, the particles can be coated by a solidified polymeric or proteinic envelop, leading to the formation of microcapsules. The profile and kinetic pattern governing the release rate of the entrapped active substance from the dosage form depend on the nature and morphology of the coated particles, which need to be established irrespective of the manufacturing method used.

Microencapsulation techniques are normally used to enhance material stability, reduce adverse or toxic effects, or extend material release for different applications in various fields of manufacturing.

Until now, the use of some interesting and promising therapeutic substances has been limited clinically because of their restrictive physico-chemical properties, which have required frequent administration. It is possible that these substances may become more widely used in a clinical setting if appropriate microencapsulation techniques can be designed to overcome their intrinsic conveniences.

Investigators and pharmacologists have been trying to develop delivery systems that allow the fate of a drug to be controlled and the optimal drug dosage to arrive at the site of action in the body by means of novel microparticulate dosage forms. During the past two decades, researchers have succeeded in part in controlling the drug-absorption process to sustain adequate and effective plasma drug levels over a prolonged period of time by designing delayed- or controlled-release microparticulate-delivery systems intended for either oral or parenteral administration.

The ultimate objective of microparticulate-delivery systems is to control and extend the release of the active ingredient from the coated particle without attempting to modify the normal biofate of the active molecules in the body after administration and absorption. The organ distribution and elimination of these molecules will not be modified and will depend only on their physicochemical properties. On the other hand, nanoparticulate-delivery systems are usually intended for oral, parenteral, ocular, and topical use, with the ultimate objective being the alternation of the pharmacokinetic profile of the active molecule.

In the past decade, ongoing efforts have been made to develop systems or drug carrier capable of delivering the active molecules specifically to the intended target organ, while increasing the therapeutic efficacy. This approach involves modifying the pharmacokinetic profile of various therapeutic classes of drugs through their incorporation in colloidal nanoparticulate carriers in the submicron size range such as liposomes and nanoparticles. These site-specific delivery systems allow an effective drug concentration to be maintained for a longer interval in the target tissue and result in decreased side effects associated with lower plasma concentrations in the peripheral blood. Thus, the principle of drug targeting is to reduce the total amount of drug administered, while optimizing its activity. It should be mentioned that the scientific community was skeptical that such goals could be achieved, since huge investments of funds and promising research studies have in many cases resulted in disappointing and nonlucrative results and have also been slow in yielding successfully marketed therapeutic nanoparticulate dosage forms. With the recent approval by health authorities of a few effective nanoparticulate products containing antifungal or cytotoxic drugs, interest in colloidal drug carriers has been renewed.

A vast number of studies and review as well as several books have been devoted to the development, characterization, and potential applications of specific microparticulate- and nanoparticulate-delivery systems. No encapsulation process developed to date has been able to produce the full range of capsules desired by potential capsule users. Few attempts have been made to present and discuss in a single book the entire size range of particulate dosage forms covered in this book. The general theme and purpose here are to provide the reader with a current and general overview of the existing micro- and nanoparticulate-delivery systems and to emphasize the various methods of preparation, characterization, evaluation, and potential applications in various areas such as medicine, pharmacy, cosmetology, and agriculture. The systematic approach used in presenting the various particulate systems should facilitate the comprehension of this increasingly complex field and clarify the main considerations involved in designing, manufacturing, characterizing, and evaluating a specific particulate-delivery system for a given application or purpose. Thus, the chapters, which have been contributed by leading authorities in the field, are arranged logically according to the methods of preparation, characterization, and applications of the various particulate-delivery systems.

The first chapter is by C. Thies, a renowned scientist in the field of microencapsulation techniques. To provide an idea of which process is most appropriate for a

specific application, the general principles of several microencapsulation processes are summarized and reviewed. This chapter focuses primarily on processes that have achieved significantly commercial use. S. Magdassi and Y. Vinetsky present an interesting technique of oil-in-water emulsion microencapsulation by proteins following adsorption of the protein molecules onto the oil–water interface. J. P. Benoit and Drs. H. Marchais, H. Rolland, and V. Vande Velde have contributed a chapter on advances in the production technology of biodegradable microspheres. This chapter deals mainly with the preparation and use of microspheres. The potential of the various technologies addressed is also discussed, with an emphasis on marketed products or those products currently under clinical evaluation. A. Markus demonstrates in his chapter the importance of applying microencapsulation techniques in the design of controlled-release pesticide formulations to meet the multifaceted demands of efficacy, suitability to mode of application, and minimal damage to the environment. The nanoparticulate-delivery systems are introduced by a chapter, authored by myself, B. Magenheim, and P. Wehrlé, that explains factorial design in the development of nanoparticulate systems. This chapter illustrates the application of the experimental design technique not only for optimization but also for elucidation of the mechanistic aspects of nanoparticle formation by spontaneous emulsification.

The second part of the book, which focuses on the evaluation and characterization of the various particulate-delivery systems, starts with an important chapter on microspheres morphology by J. P. Benoit and C. Thies. The chapter helps to clarify definitions and differences, which are very often confused. In addition, the chapter illustrates how morphology can be characterized by using different techniques. C. Washington provides his valuable expertise in the presentation of the various kinetic models used to characterize drug-release profiles from ensembles or population of microparticulate-delivery systems. It is worth noting that the release mechanism of a drug from multiparticulate systems such as microcapsules or microspheres cannot be identified by a study of global release profiles, since it has been shown that overall or cumulative release profiles form ensembles of microcapsules are entirely different from those of single microcapsules. The discrepancy arises from the heterogeneous distribution of the parameters determining release behavior in individual microcapsules, which is beyond the scope of the present chapter. The following chapter, by P. Couvreur, G. Couarraze, J. -P. Devissaguet, and F. Puisieux, presents a very detailed explanation of the preparation and characterization of nanoparticles. The authors first clearly define the morphology of nanocapsules and nanospheres, providing the background, information, and guidelines for choosing the appropriate methods for a given drug to be encapsulated.

K. Westesen and B. Siekmann have contributed an important chapter on biodegradable colloidal drug–carrier systems based on solid lipids. These new colloidal carriers different from the other well-known and widely investigated lipidic colloidal carriers, including liposomes, lipoproteins, and lipid or submicron oil-in-water emulsions by exhibiting a solid physical state as opposed to the liquid or liquid crystalline state of the above-mentioned and well-known lipidic colloidal carriers. The authors present different methods of preparation and point out the advantages of the novel dosage forms such as biodegradability, biocompatibility, ease of manufacture, lack of drug leakage, and sustained drug release. Despite three decades of intensive research on liposomes as drug-delivery systems, the number of systems that have undergone clinical trials and become products on the market is quite modest. Even though there have been few successes with liposomes, the need for drug-delivery systems is as acute as ever, and the potential that liposomes hold, although somewhat

tarnished, has not been substantially diminished according to R. Margalit and N. Yerushalmi. An interesting and original approach is presented in their chapter on the pharmaceutical aspects of liposomes. Propositions are presented on how at least some of the hurdles in research and development can be overcome and in furthering the substantial strides that have been made in advancing liposomes from the laboratory to the clinic. An ingenious solution on how the drawbacks of liposomes in vivo can be overcome is presented by D. Lasic in the chapter on stealth liposomes. He explains how the stability of liposomes in liposomicidal environments of biological systems presented a great challenge, which was only recently solved by coupling polyethylene glycol to the lipid molecules. An example of the potential of niosomes (a colloidal vesicular system prepared from nonionic surfactants) for the topical application of estradiol is contributed by D. A. van Hal and J. A. Bouwstra, and H. E. Junginger. Niosomes have been shown to increase the penetration of a drug through human stratum corneum by a factor of 50 as compared with estradiol saturated in phosphate buffer solution, making this colloidal carrier promising for the transdermal delivery of drugs.

In the third part of the book, the potential applications of the various particulate-delivery systems are presented. The methods of preparation of microcapsules by interfacial polymerization and interfacial complexation and their applications are discussed by T. Whateley, an extremely knowledgeable scientist in this field. The fast-growing field of lipid microparticulate-delivery systems, particularly lipospheres, is explained and discussed by A. J. Domb, L. Bergelson, and S. Amselem. Lipospheres represent a new type of fat-based encapsulation technology developed for the parenteral delivery of drugs and vaccines and the topical administration of bioactive compounds. In their comprehensive and exhaustive chapter, N. Garti and A. Aserin underline the potential of pharmaceutical application of emulsions, multiple emulsions, and microemulsions, and emphasize the progress made in the last 15 years in understanding mechanism of stabilization of these promising liquid dispersed-delivery systems that open new therapeutic possibilities.

J.-C. Leroux and E. Doelker and R. Gurny in their chapter on the use of drug-loaded nanoparticles in cancer chemotherapy cover the developments and progress made in the delivery of anticancer drugs coupled to nanoparticles, and the interactions of the latter with neoplastic cells and tissues. This is probably the most promising and encouraging application of nanoparticles and by far the most advanced in the process of development into a viable commercial pharmaceutical product. G. Redziniak and P. Perrier have contributed a chapter on the cosmetic application of liposomes that have been successfully exploited over the last decade. To complete the whole range of applications of capsular products, a final chapter, by M. Seiller, M.-C. Martini, and myself, discusses cosmetic uses of vesicular particulate-delivery systems. Cosmetics are definitely the largest market, as manufacturers have demonstrated that marketed cosmetic products containing these vesicular carriers and tested by dermatologists improve cutaneous hydration and skin texture, increase skin glow, and decrease wrinkle depth. It is not taken for granted that liposomes and other vesicular carriers represent a major step in cosmetics formulation. However, this field requires numerous research studies coupled with strict controls.

It is my hope that the scientific information contained herein will modestly contribute to a better understanding of the various particulate systems of all sizes that are now available and to an improved comprehension of their current and potential applications.

Simon Benita

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Contents

Preface to the Second Edition iii
Preface to the First Edition v
Contributors xv

PART I: METHODS OF ENCAPSULATION AND ADVANCES IN PRODUCTION TECHNOLOGY

1. Biodegradable Microspheres: Advances in Production Technology 1
Frédéric Tewes, Frank Boury, and Jean-Pierre Benoit
Introduction 1
Techniques Using Organic Solvents 2
Techniques Without Organic Solvents 8
References 41

2. Advances in the Technology for Controlled-Release Pesticide Formulations 55
Arie Markus and Charles Linder
Introduction 55
Standard Microencapsulation Processes for Pesticides 59
Advances in Encapsulation Technologies 67
Quality Control 71
Case Study: De-Bugger® 75
Summary 75
References 76

3. Multiparticulate Pulsatile Drug Delivery Systems 79
Till Bussemer and Roland Bodmeier
Introduction 79
Pulsatile Systems 83
Site-Specific Systems 84
Time-Controlled Pulsatile Systems 86

Multiparticulate Systems 87
Outlook 94
References 94

4. Microencapsulation Techniques for Parenteral Depot Systems and Their Application in the Pharmaceutical Industry *99*
Thomas Kissel, Sascha Maretschek, Claudia Packhäuser, Julia Schnieders, and Nina Seidel
Introduction 99
Biodegradable Polymers 100
Phase Separation and Coacervation 103
W/O/W-Double Emulsion Technique 106
Spray Drying 113
Conclusion 118
References 118

5. Coupling Methods to Obtain Ligand-Targeted Liposomes and Nanoparticles *123*
Leila Bossy-Nobs, Franz Buchegger, Robert Gurny, and Eric Allémann
Introduction 123
Liposomal Modification Techniques 124
Labeling Polymeric Nanoparticles with Ligands 138
How to Choose the Coupling Method 141
Concluding Remarks 142
References 142

6. Industrial Technologies and Scale-Up *149*
François Puel, Stéphanie Briançon, and Hatem Fessi
Introduction 149
Emulsification Processes 152
Scale-Up Approach: The Case of Emulsification 164
Applications—Examples 167
Summary 178
Notations 178
References 179

PART II: EVALUATION AND CHARACTERIZATION OF MICRO- AND NANOPARTICULATE DRUG DELIVERY SYSTEMS

7. Drug Release from Microparticulate Systems *183*
Shicheng Yang and Clive Washington
Introduction 183
Measurement of Drug Release 183
Mechanisms of Drug Release 186
Drug Release Kinetic Models 188

Empirical Models and Comparison of Drug Release Profiles 198
In Vitro–In Vivo Correlation 203
Summary 204
References 205

8. Manufacture, Characterization, and Applications of Solid Lipid Nanoparticles as Drug Delivery Systems *213*
Heike Bunjes and Britta Siekmann
Introduction: The Rationale of Using Biodegradable, Nanoparticulate Solid Lipids in Drug Delivery 213
Manufacturing Methods for Lipid Nanoparticle Suspensions 216
Physicochemical Characterization of Colloidal Lipid Suspensions and Nanoparticles 230
Applications in Drug Delivery 242
Conclusions 255
References 257

9. Amphiphilic Cyclodextrins and Microencapsulation *269*
Erem Memişoğlu-Bilensoy, A. Atilla Hincal, Amélie Bochot, Laury Trichard, and Dominique Duchêne
Introduction 269
Cyclodextrins and Derivatives 270
Amphiphilic Cyclodextrin Nanoparticles 278
Conclusion 291
References 291

10. Lipospheres for Controlled Delivery of Substances *297*
Abraham J. Domb
Introduction 297
Preparation of Lipospheres 298
Physical Characterization of Lipospheres 299
Applications of Lipospheres 302
Summary 314
References 315

11. Pharmaceutical Aspects of Liposomes: Academic and Industrial Research and Development *317*
Rimona Margalit and Noga Yerushalmi
Introduction 317
Liposomes: Definition, Needs for, and Outline of their Advantages and Drawbacks 318
Selection of the Liposome Type/Species: Views and Criteria from Academic and Industrial Research and Their Proposed Integration 323

Targeted/Modified Liposomes: An Interesting and Exciting Scientific Tool, But Can They Be Made into Products (Especially Immunoliposomes)? 326
Liposomes as a Sterile, Pyrogen-Free System with Pharmaceutically Acceptable Shelf-Life, Stability, and Dosage Forms 330
Liposome Characteristics (Percentage of Encapsulation, Kinetics of Release, Biological Activity)—In Basic Research and in Quality Assurance 333
Summary and Prospects 340
References 340

12. Microemulsions for Solubilization and Delivery of Nutraceuticals and Drugs *345*
Nissim Garti and Abraham Aserin
The Rationale 345
Microemulsions as Nanovehicles 348
Part I—Microemulsion Preparation and Microstructures 349
Part II—Potential Applications 385
Final Remarks 414
References 416

PART III: APPLICATIONS OF PARTICULATE DELIVERY SYSTEMS

13. Self-Emulsifying Oral Lipid-Based Formulations for Improved Delivery of Lipophilic Drugs *429*
Jean-Sébastien Garrigue, Grégory Lambert, and Simon Benita
Definition 429
Introduction 430
Drug Delivery Issues 430
Composition of SEDDS 433
Characterization of SEDDS 444
Biopharmaceutical Aspects 448
The Story of Oral Cyclosporin A 466
The Oral Paclitaxel Challenge 468
Future and Prospects 469
References 470

14. Recent Advances in Heparin Delivery *481*
Nathalie Ubrich and Philippe Maincent
Introduction 481
Blood and Mechanism of Action of Heparins 482
Evaluation of Heparin Efficiency 483
Oral Delivery of Heparins 483
Conclusion 516
References 516