CRC

LIPOSOME TECHNOLOGY

Interactions of Liposomes with the Biological Milieu

Edited by

GREGORY GREGORIADIS

Volume III

2nd Edition

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PREFACE

The evolution of the science and technology of liposomes as a drug carrier has undergone a variety of phases which I was privileged to witness from the very beginning. Before that, lamellar structures of lipid-water systems as models of biomembranes were studied and interpreted in terms of dynamic properties (e.g., phase transition; fluidity and change to other mesotropic entities)[1] and solute sequestration and release characteristics.[2] The latter prompted[3] the development of the liposome drug carrier concept and in 1970 animals were, for the first time, injected with liposomes containing a variety of potentially therapeutic agents.[4-6] This culminated twenty-odd years later in the first injectable liposome-based drug formulation (Vestar's AmBisome®) to be licensed in the western world for use in humans.

It has often been asked why has it taken so long and so much effort to bring a liposomal drug into the market. The question appears legitimate. However, the issue here is not the development of a new drug (which by itself can easily take quite a few years) but, rather, the development of an approach (i.e., the use of a delivery system) to improve the efficacy of a large number of existing drugs. The liposome was adopted as a promising delivery system because its organized structure could accommodate drugs in the aqueous or lipid phase, depending on their solubility. In retrospect, it is not surprising that following initial *in vivo* work with liposomes containing therapeutic agents, several potential problems became apparent. First, although it was encouraging to note[4-6] that entrapped enzymes, proteins, and lipid soluble agents by and large acquired the carrier's pharmacokinetics, water-soluble drugs of small molecular weight leaked[6] extensively into the circulating blood. Secondly, there was rapid and quantitative interception of liposomes and their contents by the tissues of the reticuloendothelial system (RES) through endocytosis,[5,7] an event which appeared to limit the use of the system to, at best, treating intralysosomal diseases. Equally disconcerting were low drug entrapment values, vesicle size heterogeneity, and poor reproducibility and instability of formulations. Yet, interest in liposomes, especially among academic workers, spread rapidly.[8,9] I attribute this to the remarkable structural versatility of the system which could, in turn, allow the design of countless liposome versions to satisfy particular needs in terms of both technology and optimal function *in vivo*.

In the ensuing years, great strides[10] were made toward the understanding of the interaction of liposomes with the biological milieu at the molecular and cellular level. As a result, ways were found to improve liposomal stability in biological fluids so that drugs would not leak significantly, and to extend vesicle presence in the circulation and targeting to alternative sites. At the same time important advances in liposome technology, exemplified by the first breakthrough in efficient solute capture,[11] provided evidence that many

of the difficulties with entrapment and stability on storage could be overcome. Indeed, optimism generated by such progress led to the foundation of at least three liposome companies in the early 1980s, encouraging ideas and enthusiasm forcefully into the path of the realities of industrial research and development, which led eventually to useful products. However, the contribution that liposome research has made (and will make) to targeted drug delivery is not just the happy prospect of additional liposome-based drugs. More importantly, it is the wealth of information that has become available on the ways the body interacts with drug carriers, and the harnessing of such information to circumvent anatomical and physiological barriers to optimal carrier performance. This cannot but prove instrumental in our efforts to ensure that old and new drugs act effectively.

Progress made in over two decades of liposome research is largely due to developments in liposome technology; early achievements were included in the first edition of this book.[12] The avalanche of new techniques that paralleled the great expansion of liposomology during the second decade has necessitated their inclusion into a larger and radically updated second edition. Indeed, such is the enormity of the new material that very little, if anything, in the first edition has been retained. As in the first edition, contributors were asked to emphasize methodology experienced in their own laboratories since reviews of methodologies with which contributors have no personal experience were likely to be superficial for the purposes of the present book. In some cases, however, overviews were invited when it was deemed useful to reconnoiter distinct areas of technology or introduce a cluster of chapters. A typical chapter incorporates (1) an introductory section directly relevant to the author's subject with concise coverage of related literature; (2) a detailed methodology section describing experiences from the author's laboratory and examples of actual applications of the method presented; (3) a critical discussion to enable the reader to appreciate the advantages and disadvantages of the method and compare it with those described by other workers. The seventy chapters contributed have been distributed logically into three volumes. Volume I deals with a variety of methods for the preparation of liposomes and a large array of auxiliary techniques required for liposome characterization. Volume II describes procedures for the incorporation into liposomes of a number of drugs, selected either for their relevance to current trends in liposome applications, or because they represent groups of drugs with similar physical properties. Finally, Volume III is devoted to technologies yielding liposomes that can function in a "targeted" fashion and to approaches of studying the interaction of liposomes with the biological milieu.

It has again been a pleasure for me to undertake this task of bringing together so much knowledge, experience, and wisdom provided generously by liposomologist friends and colleagues. It is hoped that the book will prove useful to everyone, especially those who have entered the field recently and

need a guided passage through the vastness of related literature and the complexity and diversity of aspects of liposome use. I take this opportunity to thank my research associate, Brenda McCormack for her many hours of editorial help, and CRC Press personnel for their truly professional cooperation.

Gregory Gregoriadis
London, May 1992

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Dedicated
to my parents, Christos and Athena
and my sister, Eva

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