Chapter 3
Liposomes:
Concept and Therapeutic Applications

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ABSTRACT

The science of liposomes has expanded in ambit from bench to clinic through industrial production in thirty years since the naissance of the concept. This chapter makes an attempt to bring to light the impregnable contributions of great researchers in the field of liposomology that has witnessed clinical success in the recent times. The journey which began in 1965 with the observations of Bangham and further advances made en route (targeting/stealthing of liposomes) along with alternative and potential liposome forming amphiphiles has been highlighted in this chapter. The authors have also summarised the conventional and novel industrially feasible methods used to formulate liposomes in addition to characterisation techniques which have been used to set up quality control standards for large scale production. Besides, the authors have provided with an overview of primary therapeutic and diagnostic applications and a brief insight into the in vivo behaviour of liposomes.

INTRODUCTION AND BACKGROUND

A Historical Perspective

The advent of liposomology in the domain of nanoscience has revolutionised clinical therapy in the recent times (Lian & Ho, 2001). 'Liposomes', now a benchmark in drug delivery science, was conceptualized by Alec Bangham as 'multilamellar smectic mesophases' in the year 1964(Deamer, 2010). These bilayer structures were serendipitously observed by Bangham in the process of artificially emulating cell membranes while investigating properties of cellular constituents of blood. They were formerly referred to as 'Banghasomes'. Gerald Weissmann suggested the term 'liposomes' to describe microscopic vesicles composed of one or more lipids (Sessa & Weissmann, 1968).

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Jointly with Horne, Bangham demonstrated the existence of multilamellar phospholipid vesicles through electron micrographs (A. D. Bangham & Horne, 1964). His pioneering work ascertained that lipids were the primary permeability barrier to ions and large molecules (A. BanghamStandish & Weissmann, 1965; A. BanghamStandish & Watkins, 1965) following which scientists like Gregory Gregoriad is extrapolated the concept of liposomes to drug delivery in the 1970s (Gregoriadis, 1976a, 1976b). This led to a dissemination of liposomal systems into cell biology, medicine, chemistry and biophysics.

Twenty years after the introduction of liposomes to drug delivery, the pharmaceutical industry witnessed a paradigm shift with USFDA approval of Doxil™ (Alza Corporation) in the year 1995 (Weissig, 2010). It was the first marketed injectable liposomal formulation that corroborated the prescience of Bangham and associated scientists. This journey of liposomes from bench to clinic cannot disparage the efforts of Gregoriadis, Ryman, Weissmann and Papahadjopoulos who embarked upon the application of liposomes in drug delivery and formulation sciences. Following this, the subsequent years saw a precipitous rise in the number of patents and research articles emerging in the arena of liposomology and its applications in drug delivery.

Further investigations carried out to establish liposomes in the clinic emphasized on problems like inadequate comprehension of liposomal stability, circulation time *in vivo*, lipid-drug interactions and lipid-cell interactions (Lian & Ho, 2001). A consequent milestone in this field was laid by the work of Crowes who highlighted the potential of liposomes to be freeze dried and reconstituted. The invincible efforts of researchers like Gregoriadis, Papahadjopoulos, Lasic and their team led to the landmark discovery of long circulating liposomes, wherein, they tested the antitumour efficacy of polymer bearing lipids *in vivo* (Lasic & Martin, 1995).

Given the background of the discovery of liposomes and the work carried out towards the growth of this discipline in delivery science, we would like to draw the reader's attention to how liposomes came into being much before they were discovered (Lasic & Barenholz, 1996). The use of liposomes dates back to the prehistoric man when eggs, which contain lecithin and cholesterol, were beaten in water. Virchow, in 1854, first described the swelling of lipids that he observed after transferring nerve cores in water. Later, many others like Lehmann (1911) and Reinitzer, who discovered liquid crystals, made similar observations, but failed to realize the presence of liposomes. In the course of analysing the cell structure and its constituents, Gortel and Wendelin 1926, introduced the concept of bilayered structure of cell membranes. This was followed by Danielli and Davson, who familiarised the world with the existence of a sandwich of proteins between the bilayers in 1935. Singer and Nicholson subsequently instituted the theory of the fluid-mosaic model. However, it was Bangham who comprehended the presence of an enclosed aqueous phase within the liposomes and thus laid the foundation for innovation in various disciplines.

Liposomes: Concept and Practice

In accordance with the observation of Bangham, liposomes are defined as microscopic spheres consisting of lipid bilayers encompassing an aqueous core. These vesicular structures are colloidal in nature and form when natural or synthetic phospholipids are dispersed in water. Phospholipids are amphiphilic in nature and consist of a hydrophilic head group and a hydrophobic hydrocarbon chain. When dispersed in water, the phospholipid molecules assume different morphologies depending on the phospholipid: water ratio