Review

Liposomes and Beyond: Pioneering Vesicular Systems for Drug Delivery

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Liposomes and Beyond: Pioneering Vesicular Systems for Drug Delivery

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Abstract: Vesicular drug delivery systems, especially liposomes, have revolutionized the pharmaceutical scenario with massive improvements in drug targeting, bioavailability, and controlled release. We trace the historical development and progress of liposomes as well as other novel vesicular systems such as archaeosomes and glycerosomes in therapeutic applications and present their evolution from liposomes to these advanced systems highlighting their structural differences, strategies for formulation, and potentials for targeted drug delivery. We also outline some of the significant events in the development and commercialization of liposomes and examine a few of the FDA-approved formulations, like Doxil and Ambisome, that exemplify clinical success. Other up-and-coming trends are the use of archaeosomes for vaccine delivery and glycerosomes for topical and oral delivery. The scaling problems, consistency of manufacture, and regulatory problems, however, remain with these liposomal formulations. The paper also ends with the potential in the future of such delivery systems, especially as nano-technology and personalized drugs are being integrated with it thereby indicating a transformative effect in determining the future of drug delivery. In the course of this review, we emphasize continued innovation and optimization in the vesicular drug delivery systems to achieve their full therapeutic potential.

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- Manufacturing challenges and scalability.
- Regulatory hurdles for novel vesicular systems.
- Future directions and emerging opportunities in vesicular drug delivery.

1. Introduction to Liposomal Technology

1.1. Historical Perspective of Liposomal Development

The history of liposomal technology dates back to early 1960, since the foundational work was in 1964 from Bangham and Horne, discovering that, under hydration conditions, phospholipids spontaneously form bilayer structures capable of entraping aqueous substances-that was, essentially, a discovery of liposomes as lipid vesicles [1]. The significant finding was a tremendous progression of understanding for lipid bilayers but has formed an essential basis for development toward liposomal drug delivery.

Soon after, Gregoriadis (1973) published further work on liposomes as drug carriers. His paper proved that liposomes are excellent encapsulating and drug delivery systems for both hydrophilic and lipophilic drugs, which presents it as a versatile and biocompatible drug delivery vehicle [2]. This marked the beginning of liposomes as delivery vehicles for therapeutic agents, especially those which are poorly soluble in water or have poor pharmacokinetic profiles.

1.2. Key Milestones in Liposome Research and Commercialization

That indeed had a brilliant beginning with the introduction of Doxil, or liposomal doxorubicin, considering the first FDA approval in the 1990s for the same. Indeed it was a brilliant advancement into clinical applications for liposomal technology. This drug was approved by the FDA for its use in ovarian cancer treatment in the year 1995 and other cancers; thus, it was proved to be the application of liposomal formulation to make the drug practically suitable to reduce side effects for improvement in efficacy [3]. This success opened more doors for clinical practices involving other liposomal formulations.

Most of the developments of the following decades about the liposome technology had taken place when people realized much better drug delivery systems with targeting sites more appropriately. The biggest leap into was the concept of polyethylene glycol modification, whereby increased circulation time in blood with liposomes increased efficiency through their carrying of drugs even further. These types of alterations could further facilitate the capability of liposomes to escape the immune system, making drugs target tissues in an even better and effective way.

This raised interest in formulating into the form of liposomes, the therapeutic applications drifted away from oncology towards infectious diseases and vaccine delivery. FDA approval on the safety and efficacy of liposomes as a drug delivery vehicle opened floodgates for many varied liposome-based treatments. Liposomes are now considered an established drug delivery technology with many different formulations available in the marketplace, thus opening up new therapeutic opportunities for a wide range of diseases [4].

As states Sengar, 2023, ways for the targeting precision as well as efficiency of drug-delivery systems through a liposome are under investigations within this area itself. Focus in the development process through liposome targeted drugs were aimed at cells or tissue levels. This strategic planning aimed to overcome all inhibiting factors for maximal achievable success in therapies [4].

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2. Evolution of Vesicular Systems in Therapeutic Applications

2.1. Advancements from Liposomes to Novel Vesicular Systems

Lipsome has been the basis of vesicular drug delivery over the centuries, but the limitations associated with it, including instability, early clearance, and a low loading capacity, are making alternative systems of vesicles an attractive choice. For a good number of decades, advancements made from liposomes to higher order carriers had provided enhanced results in the therapeutic outputs.

Early modifications were done on liposomes to improve shelf life and circulation time. Such modifications, including PEGylation, greatly enhanced the pharmacokinetics of the liposomes, hence making it possible for the liposomes to avoid the immune system and increase half-life in circulation [5]. But all these advancements mean that not all drugs can be given in liposomes; particularly proteins, peptides, and hydrophobic compounds might require alternative carriers.

These new challenges postulated the emergence of vesicular systems such as archaeosomes and glycerosomes. These new vesicular systems, have been introduced to the application field. Archaeosomes: These are the lipid vesicles obtained from extremophilic archaeal organisms, with stability at extreme conditions and thus, highly useful in oral delivery and vaccines applications. Glycerosomes are hybrid vesicles that have the advantages of both liposomes and glycerol, increasing the solubility of hydrophobic drugs besides enhancing drug permeation through the skin for topical applications [6,7].

Besides, the need to develop more efficient targeted and controlled drug delivery has fueled advanced nanoparticles as well as other advanced vesicular systems. Nanoparticles owing to their unique features- size-dependent drug release with ease of functionalization-were able to open doors to the much greater precision in the delivery of drugs [8].

2.2. Emerging Trends: Archaeosomes, Glycerosomes, and More

As the field of vesicular drug delivery has advanced, emerging systems such as archaeosomes and glycerosomes have gained attention due to their superior properties over traditional liposomes. Archaeosomes, which utilize lipids derived from archaeal organisms, are known for their increased stability and resistance to physical and chemical degradation, making them suitable for the delivery of sensitive drugs, particularly those used in vaccines and immunotherapy [5]. Their unique composition allows for better encapsulation and release profiles when compared to conventional liposomes, particularly in harsh environments.

Glycerosomes, developed by combining glycerol with traditional lipid-based vesicles, represent another innovation in vesicular drug delivery systems. These vesicles are particularly effective in enhancing the skin penetration of drugs, making them ideal candidates for transdermal delivery. Glycerosomes have been increasingly used for topical drug formulations, especially those targeting the dermal layers for the treatment of skin conditions or for local drug release [6].

The shift from traditional liposomes to these novel systems reflects the growing understanding of how vesicular carriers can be tailored for specific applications. Innovations such as glycerosomes and archaeosomes are particularly beneficial in fields like cancer therapy, gene delivery, and vaccine development, where controlled release and stability are paramount. Furthermore, nanoparticles have made it possible to achieve precision drug delivery, thereby reducing side effects and enhancing the therapeutic effects of drugs [7,8].

3. Comparative Analysis of Liposomes, Archaeosomes, and Glycerosomes

3.1. Structural Differences and Formulation Strategies

Liposomes, archaeosomes, and glycerosomes have different structural properties. The differences of their structural properties affect them in their use in diverse multiple drug delivery applications. It is a bilayered spherical vesicle made from phospholipids. They trap both hydrophilic

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as well as hydrophobic drugs. Its preparation involves techniques such as thin-film hydration, ethanol injection, and reverse-phase evaporation [9,10].

Archaeosomes differ significantly from the lipid composition of archaea. It contains ether bonds and isoprenoid chains, which makes it more resistant to oxidative and hydrolytic degradation, thus more robust against extreme conditions. Glycerosomes contain glycerol in the lipid bilayer that enhances the fluidity of the membrane along with drug solubility. Such a special composition makes them highly useful for the transdermal delivery of drugs through this route [11,12].

3.2. Advantages and Limitations of Each Vesicular System

3.2.1. Liposomes

The most used because they are biocompatible and diverse. Liposomes control the delivery of the drug. It could be targeted in nature and not toxic at all. Their stability is an issue; it aggregates during storage and even oxidize [9].

3.2.2. Archaeosomes

Archaeosomes have better stability, even in extreme conditions. For oral and vaccine delivery purposes, archaeosomes are fine, but the mass production is not feasible, hence the production cost will be relatively high [10,13].

3.2.3. Glycerosomes

Glycerosomes are useful where permeability has to be enhanced, and that is beneficial in the field of dermatological formulations. However, structural integrity may not be the best for long-term systemic drug delivery applications [12,14].

Table 1. Comparison of Liposomes, Archaeosomes, and Glycerosomes.

Vesicular System	Advantages	Challenges	Applications
Liposomes	Biocompatible and versatile; controlled drug release, targeted delivery, minimal toxicity.	Prone to aggregation and oxidation during storage [9].	Widely used for various drug delivery applications.
Archaeosomes	Superior stability, particularly in harsh environmental conditions.	High production costs and limited scalability [10,13].	Ideal for oral and vaccine delivery.
Glycerosomes	Enhanced permeability, suitable for dermatological formulations.	May lack structural integrity for long-term systemic drug delivery [12,14].	Effective in dermatological and transdermal applications.

3.3. Suitability for Specific Drug Delivery Applications

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Liposomes have been quite widely used in cancer therapy where formulations of Doxil and Ambisome have already been approved by the FDA. Vaccines fall under the applications of archaeosomes, and stability plus the initiation of an immune response can easily be accomplished. Glycerosomes find special application in the transdermal delivery system. There have been cases of drug delivery through transdermally, drugs like hormones and anti-inflammatory drugs successfully delivered [13,14].

Table 2. Suitability of Vesicular Systems for Specific Drug Delivery Applications.

Vesicular System	**Applications**	**Examples**	**Key Features**
Liposomes	Cancer therapy.	FDA-approved formulations: Doxil, Ambisome.	Efficacy in delivering chemotherapeutic agents.
Archaeosomes	Vaccine delivery.	Preclinical studies have demonstrated archaeosome-based vaccines inducing robust immune responses against pathogens like Listeria monocytogenes and in cancer models.	Stability and immune activation.
Glycerosomes	Transdermal and topical delivery systems.	Effective delivery of anti-inflammatory agents and hormones.	Enhanced permeability through the skin.

4. Clinical Applications and Approved Products

4.1. Overview of FDA-Approved Liposomal Formulations

Liposomal formulations, such as Doxil (doxorubicin liposome), and Ambisome (amphotericin B liposome), have altered drugs delivery landscape with augmentation in therapeutic efficacy through minimal systemic toxicity. Doxil, approved in the treatment of ovarian cancer, AIDS-related Kaposi's sarcoma, and multiple myeloma, exhibits a prolonged circulation time in addition to targeted delivery to tumor sites [15,16].

It has been used in systemic mycoses and visceral leishmaniasis where the ambisome encapsulates hydrophobic drugs within a biocompatible carrier by liposomes. This creates a benchmark in antifungal therapy that is very stable with less nephrotoxicity [16,17].

4.2. Archaeosomes in Vaccine Development

Archaeosomes derived from archaeal lipids have emerged as some promising candidates for the vaccine delivery system. Their resistance to extreme environmental conditions, besides the fact that they induce humoral and cellular immunity, qualifies them to be appropriate candidates for use in

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infectious disease and cancer vaccines. Glycerosomes have been quite extensively researched in relation to antigen and adjuvant delivery; it increased the immunogenicity up to several fold [17,18].

4.3. Glycerosomes for Dermatological and Oral Delivery Systems

Glycerosomes are the new generation of vesicles where glycerol is entrapped within the bilayer. Glycerosomes were subsequently shown to exhibit excellent performance as a novel carrier system for transdermal and oral drug delivery, which can be focused to deliver anti-inflammatory agents effectively while also improving hydration of the skin. The newer research even suggests that their future development might allow incorporating the hydrophilic drugs for systemic effects to amplify their clinical utilities [15,19].

5. Challenges and Perspectives

5.1. Manufacturing Challenges and Scalability

The main problem with **scaling up such vesicular drug delivery** systems as liposomes lies in the inherent complexity associated with the maintenance of quality and integrity of the system when scaled up, with passage from the laboratory scale to the industrial scale. In this regard, one such issue is the size uniformity of the large batches of vesicles. At a low level of production, the size of liposomes or any vesicle can be easily managed. But in bulk preparation, this is difficult and leads to difficulties in obtaining equal encapsulation of the drug, release rates, and stability [20].

The last problem **is batch-to-batch consistency**. The formation of vesicular systems depends on several parameters, including the composition of the solvent, temperature, and shear forces, which determine the final characteristics of the product. Variations in manufacturing conditions would result in variations in the size distribution of vesicles, encapsulation efficiency, and drug release profiles, thereby giving problems in regulatory approval and clinical efficacy [22].

Another serious problem with mass production is contamination. Liposomal and vesicular formulations are highly susceptible to microbial contamination as the composition contains ingredients like phospholipids, which are very susceptible to degradation by undesirable conditions. The system used in mass manufacture has to be sterile and contamination-free at all stages of manufacture, storage, and distribution. It demands very high-sterilization techniques, filtration, and even some specialized equipment [20].

Except for technical aspects, many of the economic factors-based concerns associated with the production of manufacturers exist regarding vesicular systems commercially. Generally, the manufacturing of liposomes with high-purity lipids is difficult, and the techniques such as extrusion or sonication make it more challenging, increasing the cost of production and thereby restricting accessibility and usability in wider therapeutic applications. The formulation of liposomes should be designed to provide long-term stability during the manufacturing process, transport, and storage. Since the physical condition such as temperature or pH has been known to affect liposomes, those may in turn affect negatively on the stability and later the therapeutic effect of the liposomes. Scalable manufacturing methods that do not compromise the integrity and quality of the formulation but manufacture it cost-effectively would become an imperative for commercializing it [22].

Table 3. Manufacturing Challenges and Scalability of Vesicular Drug Delivery Systems.

Challenge	Description	Key Issues	References
Scaling Up Production	Scaling the production of vesicular drug delivery systems, such as liposomes, is a significant challenge.	Maintaining vesicle size, batch-to-batch consistency, and preventing contamination.	[20,22]

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Cost-Effectiveness	Large-scale production often faces cost-related difficulties that affect commercial success.	High production costs and stability issues.	[20,22]

5.2. Regulatory Hurdles for Novel Vesicular Systems

It is complex to have a regulatory landscape for vesicular drug delivery systems. The FDA and EMA, among others, enforce strict regulations over formulations involving liposomes, in order to achieve the safety, efficacy, and quality of drugs. Moreover, without standardization, it appears rather troublesome when attempting to approve innovative systems like archaeosomes and glycerosomes inasmuch as they strongly require considerable preclinical as well as clinical studies ensuring biocompatibility and possible therapy benefits which, naturally are extremely time-consuming as well as resource-intensive [23–25].

5.3. Future Directions and Emerging Opportunities

Some of the areas that may be future directions for the vesicular systems may include nanotechnology and biotechnology. The use of these microfluidics methods integrated with 3D printing will make it easier in achieving higher scalability and accuracy when it comes to the production of vesicles. Other breakthrough applications would be personal medicine models, where the drug delivery systems are tailored to the profile of an individual patient. Another direction is the application of archaeosomes in immunotherapy and glycerosomes in gene delivery, which show that this system is varied in all its applications [21,24,26].

Conclusion

The evolution of vesicular drug delivery systems has taken a giant leap from the very early period of liposomal technology to present-day innovations like archaeosomes, glycerosomes, and other new vesicular systems. Liposomes were first developed as carriers for drugs in the 1960s, paving the way for increasingly sophisticated systems for targeted and controlled delivery of drugs while addressing numerous drawbacks of conventional therapy [1]. The advent of systems such as archaeosomes has further diversified their use, especially in vaccine design, while glycerosomes have shown applications in dermal and oral drug delivery [5,7]. Each of the vesicular systems has its specific advantages in terms of stability and encapsulation efficiency along with the profile of drug release. However, many challenges still restrict them to manufacturing at scale, regulatory issues, and optimization research for the specific therapeutic application [20,24].

Thus, further continuing development in these types of vesicular systems opens up stellar possibilities in improving patient outcomes across a spectrum of diseases, from oncological ailments to infectious ones. Further progress in formulation techniques, clinical testing, and regulatory approval processes will be needed to assist the full realization of the ability of these systems. Future directions will more likely be seen incorporated with nanotechnology and individualized medicine for more specific targeted and efficient therapies. Therefore, the rhizomes of vesicular systems retain the impressive prospect of the future of medicine with vast possibilities of increasing efficacy and reducing safety risks of treatments.

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