WWW.IJRPR.COM

International Journal of Research Publication and Reviews

Journal homepage: www.ijrpr.com ISSN 2582-7421

A REVIEW ARTICLE ON LIPOSOMES

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ABSTRACT :

Liposomes are nanoscale drug delivery systems composed of phospholipid bilayer vesicles that have gained significant attention in biomedical and pharmaceutical research. These vesicles can encapsulate both hydrophilic and hydrophobic therapeutic agents, allowing for controlled and sustained drug release. One of their primary advantages is targeted drug delivery, which minimizes systemic side effects and improves therapeutic efficacy. This is especially beneficial in areas such as cancer therapy, where delivering drugs directly to tumor cells can reduce damage to healthy tissues. Liposomes also play a crucial role in vaccine delivery by enhancing immune responses, and they are increasingly used in cosmetic formulations for improved skin penetration and moisturization. Furthermore, liposomes can be functionalized with targeting ligands, antibodies, or polymers to enhance site-specific delivery. Despite current challenges related to large-scale production, stability, and regulatory approval, advancements in formulation and manufacturing technologies continue to improve their viability. Liposomes hold great promise in future therapies, including gene and RNA-based treatments.

KEY WORDS
Liposomes,Drug delivery,Nanoparticles,Targeted therapy,Cancer treatment,
Controlled release,Biocompatibility,Vesicles,Liposomal delivery.

INTRODUCTION

Liposomes are spherical vesicles composed of phospholipid molecules that form a circular sac, encapsulating water droplets to transport medicine into tissue membranes. Characterized as 100 nm-sized nanoparticles, they were first described in 1961 by Bangham, who discovered them while dispersing phosphatidylcholine in water, leading to the formation of a closed bilayer structure. This term derives from the Greek “Lipos” (fat) and “Soma” (body). Liposomes are small vesicular structures with a phospholipid bilayer that serve as carriers for various medications. They can target specific areas of the body, alongside other carriers like lectins and nanoparticles. Liposomal drug delivery is gaining popularity due to its applications in drug delivery, cosmetics, and biological membrane structure. The bilayer consists of amphiphilic phospholipids like phosphatidylcholine and phosphatidyletanolamine, which feature a hydrophilic head and a hydrophobic tail, facilitating the formation of these lipid membranes.[1]

HISTORY

Dr. Alec D. Bangham, a British hematologist, discovered liposomes in the 1960s while researching cell membranes using an electron microscope. Liposomes, small spherical structures made of lipid bilayers, have transformed pharmacology by enabling targeted drug delivery and minimizing side effects through encapsulation. They have found applications in gene therapy, food technology, cosmetics, and medicine. Researchers continue to innovate by developing various liposome types with different sizes and surface modifications to enhance their utility in delivering therapeutic agents and bioactive compounds, solidifying their importance in medicine and biotechnology.[12]

LIPOSOMES

The liquid within liposomes consists of proteins, peptides, hormones, enzymes, antibiotics, antifungals, and anticancer agents. Unlike free medications that quickly reach their therapeutic levels due to metabolism and excretion, liposome-encapsulated drugs sustain their therapeutic efficacy longer, as they must first be released from the liposome. These synthetic, spherical vesicles are comprised of non-toxic phospholipids and cholesterol, making them biocompatible and effective drug delivery systems. The characteristics of liposomes are influenced by factors such as lipid content, surface charge, size, and production method, which affect the bilayer's rigidity, fluidity, and charge. For example, unsaturated phosphatidylcholine from natural sources yields more permeable and unstable bilayers compared to saturated phospholipids, like dipalmitoyl phosphatidylcholine, which form a rigid and nearly impermeable structure.

It has been shown that phospholipids, when hydrated in aqueous solutions, spontaneously form closed structures known as liposomes. These vesicles can

encapsulate lipid or aqueous medications, depending on the drug type. Liposomes, typically spherical with diameters ranging from 30 nm to several micrometers, consist of one or more phospholipid bilayer membranes. Their structure is influenced by the amphipathic nature of lipids, driving the self-assembly into bilayers where polar head groups face the aqueous environments. Liposomes can take various forms beyond the traditional bilayer shapes and serve as effective delivery systems for pharmaceutical agents. The concept of liposomes was established in the 1960s by Alec Bangham and colleagues, leading to extensive research in their application for delivering imaging agents, proteins, nucleic acids, and small molecules.[2]

Advantages

- Steady drug release
- Targeted delivery
- Stabilization of drugs in adverse environments
- Ability to transport both lipid-soluble and water-soluble drugs
- They enhance the stability of proteins, can be administered via various routes, and are beneficial for gene delivery by protecting DNA from degradation.[3]

Disadvantages

- Comprise high production costs
- Potential leakage
- Reactions of phospholipids
- Short half-life, low solubility, and challenges in sterilization and large-scale manufacturing. Additionally, liposomes may cause allergic reactions and exhibit batch variability, leading to rapid removal from circulation and instability.[4]

Method of preparation for liposomes

first, lipids are separated from organic solvents and then dispersed in an aqueous medium. The lipids are purified into liposomes, and the final product is thoroughly examined. There are techniques for both passive and active loading of drugs into liposomes. Passive loading includes three methods:

- Solvent dispersion
- Mechanical dispersion
- Detergent removal to eliminate nonencapsulated materials

The mechanical dispersion method is one of the approaches utilized.[5]

Structural components of liposomes

Phospholipids, derived from phosphatidic acid, are crucial in liposome formulation, comprising over half the weight of biological membrane lipids. Their structure includes a glycerol backbone, esterified fatty acids, and various organic alcohols such as choline and ethanolamine. Notable examples include phosphatidyl serine (PS), phosphatidyl inositol (PI), phosphatidyl choline (PC), phosphatidyl ethanolamine (PE), and phosphatidyl glycerol (PG), saturated fatty acids are preferred for stable liposome formation.

Sphingolipids, which consist of sphingosine and a fatty acid, serve as essential components found in both plant and animal cells. Their structure features multiple building blocks, including a head group that can vary in complexity. Key sphingolipids mentioned are glycosphingolipids and sphingomyelin.Grey matter contains gangliosides, contributing to liposome synthesis by providing negative charges at neutral pH through complex saccharides.

cholesterol and its derivatives, which enhance membrane stability and reduce permeability to water. Cholesterol's presence mitigates rapid interaction with plasma proteins, thereby preventing physical instability linked to the depletion of liposome monolayers. Acting as a molecular filler, cholesterol stabilizes the bilayer structure by connecting phospholipid molecules.

synthetic phospholipids such as DPPC, DSPC, DPPE, DPPS, DPPA, and DOPC, among others. The polymerization of synthetic phospholipids containing diactylenic groups under ultraviolet light creates polymerized liposomes, enhancing the permeability barriers for pharmaceuticals. The stability of liposomes is affected by the application of charged polymers, which create repulsive electrostatic interactions with macromolecules. Non-ionic, water-compatible polymers like polyethylene oxide also improve solubility. Furthermore, cationic lipids such as DOTAP and DODAB/C are mentioned, with their use in various applications emphasized.

Various lipids and surfactants can form liposomes, with single chain surfactants effectively mixed with cholesterol. Non-ionic lipids, along with polyglycerol and polyethoxylated mono and dialkyl amphiphiles, are commonly used in cosmetics. Liposomes can also be stabilized by single and double chain lipids containing fluorocarbon chains. Additionally, sterylamine and diethyl phosphate can be used to impart positive or negative surface charges to these liposomes.[6]

MECHANISM OF LIPOSOME FORMATION

A liposome is formed from phospholipids, creating a lipid bilayer that surrounds a hydrophilic core. This structure prevents hydrophilic solutes from passing through while allowing hydrophobic substances to associate with the bilayer. Liposomes can fuse with cell membranes to deliver molecules,

although this is a complex process. They are utilized as models for artificial cells and can be engineered for drug delivery in various ways, such as adjusting pH to promote drug neutrality inside the liposome, facilitating diffusion rather than direct fusion. They can also assist in biodetoxification by capturing drugs in the bloodstream. Additionally, liposomes may enhance drug delivery through endocytosis and can be modified with ligands to increase uptake by specific cells. Another application is liposome transfection for DNA delivery, along with serving as carriers for dyes in textiles.[10]

CLASSIFICATION

Classification of liposomes is based on size and shape, composition, and production methods. By size and shape, they are classified into

- Multilamellar (MLV)
- Large unilamellar (LUV)
- Unilamellar vesicles (SUVs)

Compositionally, liposomes can be conventional, pH-sensitive, cationic, long circulating, or immuno-liposomes. Their production methods include passive loading, mechanical dispersion (such as sonication, micro emulsification, lipid hydration, and French pressure cell), solvent dispersion (including ethanol and ether injection, double emulsion vesicles, and reverse phase evaporation), and detergent removal techniques like dialysis.Detergent removal techniques include mixed micellar dilution and active loading techniques.

Multilamellar vesicles (MLVs) range from 100 to 1000 nm, comprising multiple bilayers, and are produced via thin-film hydration, making them stable for long-term storage, though they are quickly cleared by the Reticulo Endothelial System (RES).

Large unilamellar vesicles (LUVs) consist of a single bilayer and can exceed 1000 nm, offering high encapsulation efficiency due to their ability to store substantial volumes of solutions. They exhibit similarities to MLVs and utilize methods such as detergent dialysis for their formulation.Ether injection and the reverse phase evaporation process create large unilamellar vesicles.

Small unilamellar vesicles (SUVs), typically smaller than 0.1 micrometers, are composed of a single bilayer and prepared using solvent injection with ether and ethanol. Liposome membranes often utilize natural components found in living cell membranes. Conventional liposomes, primarily composed of natural phospholipids, target the reticuloendothelial system (RES) and are charged, designed to shorten circulation times, and utilize a hydrophilic polymer coating to enhance longevity in circulation. These liposomes represent the first generation in pharmaceutical applications, though issues related to lipid membrane manipulation persist.

pH sensitive liposomes

pH-sensitive liposomes are composed of phosphatidyl ethanolamine, cholesterol hemisuccinate, and oleic acid, designed to release contents in acidic environments while remaining stable at physiological pH. Various types exist based on their mechanisms of pH sensitivity, primarily involving stabilizers with acidic groups.

Cationic liposomes, made from DDAB and DOGS, transfer negatively charged macromolecules like DNA and RNA but have short lifespans and high toxicity, requiring local administration. Long-circulating liposomes are enhanced with hydrophilic materials, allowing for extended circulation in the body, beneficial for tumor-targeting therapies. Immuno-liposomes, while not detailed, represent another category in this liposomal classification.

Immuno-liposomes (ILs) are created by coupling antibodies to either the lipid bilayer of liposomes with PEG chains (type 1) or to the distal ends of PEG chains (type 2). Direct coupling to the bilayer can reduce antigen binding based on PEG chain length and amount, while coupling to the PEG terminus restores binding. There are disadvantages to using whole antibodies for IL generation.

Liposomes can be classified by production method:

1) Passive loading technique involves forming liposomes during drug loading, where hydrophobic drugs are encapsulated within the lipid bilayer, often using organic solvents to create a drug-containing thin film

2) Mechanical dispersion method involves using a small percentage of swelling volume to encapsulate lipid-soluble compounds effectively while limiting the effectiveness for water-soluble compounds.

The procedure for preparing lipid layers and converting multilamellar vesicles (MLVs) into small unilamellar vesicles (SUVs). Initially, a mixture of phospholipids and charge components is prepared in a solvent of methanol and chloroform, followed by the evaporation of the organic solvent using a rotary evaporator. The lipid layer is then hydrated with saline phosphate buffer and allowed to swell, resulting in MLVs. Lastly, sonication, which employs sound waves, is used to convert MLVs into SUVs, utilizing either probe or bath sonication methods.[7]

Organoleptic findings and Nanoliposome characterisation

The study focuses on the characterization of nanoliposomes derived from the fruit extract of S. xanthocarpum. The resulting liquid was thick, brownish-green, and odourless, with no significant differences in organoleptic properties among formulations F1, F2, and F3, regardless of ultrasonication duration.

As the concentration of nanoliposome material increased, viscosity rose, while higher sonication times decreased viscosity. All formulations displayed nanoscale particle sizes of 100–200 nm, with F2 having the smallest particles. A two-way ANOVA confirmed significant differences ($P<0.05$) in viscosity, particle size (PS), polydispersity index (PDI), and zeta potential (ZP) across formulations and sonication times.

Particle distribution was consistent without aggregation, and transmission electron microscopy (TEM) indicated that F2 had the shortest average diameters. The maximum entrapment efficiency of the nanoliposomes was noted in F2 at 92.981%, with a 30-minute sonication time, which was selected for further stability testing based on measured parameters.

After 12 weeks of storage at room temperature (25 ± 2 °C), the nanoliposomes maintained their color, smell, and taste; however, phase separation occurred in formulas F1, F2, and F3. In contrast, no phase separation or organoleptic changes were observed after 12 weeks at low temperatures (4 ± 2 °C). The pH values for F1, F2, and F3 were initially 5.9, 6.1, and 6.0, respectively, with slight decreases noted at room temperature and stable values at low

temperature. The viscosity of the nanoliposomes increased over time, with significant values recorded at both temperatures for the different formulas. Overall, particle size also increased after 12 weeks under both storage conditions.[11]

EVALUATION OF LIPOSOMES

Evaluation of liposomes focuses on ensuring consistent performance for liposomal formulations in vitro and in vivo. Evaluation parameters are categorized into physical, chemical, and biological factors. Physical characterization assesses size, shape, surface properties, lamellarity, phase behavior, and drug release profiles. Chemical characterization investigates the potency and purity of lipophilic components. Biological characterization assesses the safety and therapeutic suitability of formulations, including factors like shape and lamellarity.

Electron microscopy techniques, such as Freeze Fracture Electron Microscopy and P31 Nuclear Magnetic Resonance Analysis, are utilized to assess vesicle shape and lamellarity in liposomes. Various methods exist for measuring vesicle size and distribution, including fieldlow fractionation, laser light scattering, photon correlation spectroscopy, light and fluorescent microscopy, and electron microscopy, with the latter being the most precise, albeit time-consuming. Laser light scattering provides quick average assessments of liposome properties, while atomic force microscopy allows for recent investigations into liposome appearance and stability.

Measurement techniques generally categorize into hydrodynamic, diffraction, scattering, and microscopical methods, employing strategies such as optical microscopy, cryo-TEM, and ultracentrifugation for size and shape analysis Gel-based agarose bead thin-layer chromatography serves as a quick method for estimating liposome size distribution, though its susceptibility to physical obstruction remains unclear. The encapsulation efficiency examines the capture rate of water-soluble substances in the liposome's aqueous core. Surface charge significantly affects lipid-cell interactions; while cationic liposomes facilitate membrane fusion and rapid content delivery, they are eliminated quickly post-administration. Conversely, neutrally charged liposomes are stable but interact less with cells. Hydrophilic surface coatings reduce opsonization, enhancing circulation stability compared to hydrophobic coatings, thus improving overall performance in biological environments.[8]

APPLICATIONS

- Liposomes are versatile vehicles in medicine
- Primarily used for drug and protein delivery
- They are effective in both in vivo and in vitro applications and are integral to targeted therapies for cancer, utilizing drugs like actinomycin-D and methotrexate
- Liposomes also function in pulmonary drug delivery systems via nebulizers, and they can be formulated for topical applications, incorporating medications such as corticosteroids and benzocaine
- In cell biology, liposomes aid in manipulating membrane lipid states and serve as controlled-release systems for antiviral, antifungal, and antibacterial treatments.[9]

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