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AN UPDATED REVIEW ON LIPOSOMES- A MODIFIED DOSAGE FORM

Garima Pandey, Aparna Joshi, Kapil Kumar, Vaishali Rajput

Division of Pharmaceutics, Global Institute of Pharmaceutical Education and Research, Kashipur, Uttarakhand, India.

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Abstract

The first Nano medication to be approved for clinical usage was liposomes. Liposomes are being utilized more frequently for targeted drug delivery because of their incredible capacity to prevent drug deterioration and minimize unwanted side effects. In Liposomes, the drug can either be integrated inside the aqueous space (hydrophilic drugs) or inside the phospholipid's bilayer (hydrophobic drugs). The classification of liposomes, production of liposomes, applications, their advantages and drawbacks are the main topics covered in this review. Today, most researchers are becoming more and more interested in liposomes. As they are effective against a certain condition, and are simple to make, and have several additional benefits than others. This review covered liposomes as a modified dosage form, covering their present status, drawbacks, and applications. Numerous liposome-based formulations with higher drug concentrations have been developed as liposomes are effective as therapeutic agents.

***Keywords*:** Liposomes, drug delivery, phospholipids.

***Corresponding Author**
Vaishali Rajput

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Introduction

Paul Ehrlich imagined a medicinal delivery system that would target drugs directly to the specified cells, what he called "magic bullets," and this idea launched in 1906 the era of development for targeted delivery [1]. The Greek terms 'Lipos' (fat) and 'Soma' (body) are the origin of the name 'liposome,' which is a combination of both [2]. "Liposomes are colloidal, vesicular structures made up of one or more lipid bilayers enclosing an equal number of aqueous compartments". Liposomes have lipid bilayers that resemble the plasma membrane of the cell, which makes it ideal and safe for drug administration [3].

A membranous lipid bilayer completely encloses an aqueous volume in liposomes, which are concentric bilayered vesicles structurally [4]. The liquid interior of the sphere-shaped shell contained peptides, proteins, hormones, enzymes, antibiotics, antifungal, and anticancer chemicals [5]. Liposomes are lipid based spherical shaped vesicular systems, in which a lipophilic bilayer is sandwiched between two hydrophilic layers [6]. Liposomes are capable of carrying both hydrophilic and lipophilic pharmaceuticals due to their biphasic environment or amphiphilic nature i.e. Both hydrophilic and lipophilic drugs can be transported therein.

Lipophilic drugs (log P>5) are contained within the lipid bilayer of the liposomes, whereas hydrophilic drugs (log P -0.3) reside exclusively in an aqueous domain. Drugs with an intermediate partition coefficient, or 1.7 (log P4), present a challenge for drug loading because they compromise between the lipid and aqueous layers and are vulnerable to significant leakage during storage [7].

When a drug is injected into the bloodstream, it usually reaches a therapeutic level for a short time because of metabolism and excretion. However, when a drug is encapsulated by liposomes, it stays at a therapeutic level for a longer duration because the drug needs to be released from the liposome before it can be metabolized and excreted [8].

To target the drug to a specific site, several carriers which include nanoparticles, microparticles, polysaccharides, lectins, and liposomes can be employed. Liposomal drug delivery is gaining popularity due to its contributions to a variety of fields such as drug delivery, cosmetics, and biological membrane construction. Liposomes are highly

valuable because they perform as a carrier for a broad spectrum of medicines with potential therapeutic benefits or additional characteristics. Liposomes are colloidal carriers that range in size from 0.01 to 5.0m. These are actually bilayer vesicles produced when phospholipids are hydrated in excess of aqueous medium or solution [9].

The research and development of liposomes has been one of the most important new drug delivery systems investigated by researchers. Liposomes have drawn a lot of fascination as a carrier for drug delivery. The growth of liposomal research is primarily since they mimic biological membranes, which makes them a better fit for study across multiple fields [10]. Liposomes are promising drug delivery systems due to their size, hydrophobic and hydrophilic characteristics, and their ability to encapsulate drug molecules in either the aqueous interior of the vesicles or the lipophilic membrane11. They are frequently employed as universal drug carrier systems in the pharmaceutical and cosmetic industries due to their adaptability and biocompatibility.

Structure of Liposomes

Membranes are typically composed of phospholipids. These phospholipids have a have a water-loving (hydrophilic) head and a water-repelling (hydrophobic) tail. The head is attracted to water, while the tail, made of a long hydrocarbon chain, doesn't like water9. When lipids are suspended in an excess of water, liposomes are spontaneously formed due to intrinsic interfacial chemistry that forms one or more phospholipid bilayers around a water space as colloidal dispersions.

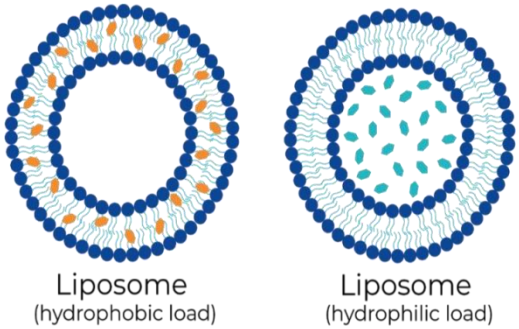

Figure 1: Structure of liposomes

Phospholipids such soybean phosphatidylcholine or synthetic dialkyl or trialkyl lipids are the main ingredients used to make liposomes. To increase the efficiency of the encapsulated medication, prolong the circulation half- life, and optimize the biodistribution profile, polymers and even membrane proteins may be used in liposomal formulations. Since cholesterol modifies membrane permeability, alters fluidity, and enhances the stability of bilayer membranes in the presence of biological fluids like blood and plasma, cholesterol must have been included in liposomes [8].

1) PHOSPHOLIPIDS: Glycerol-based phospholipids are commonly used in liposome formulations and make up more than 50% of the lipid weight in biological membranes. These phospholipids are derived from Phosphatidic acid and have a glycerol moiety as a backbone9.

   Example of phospholipids:
   - Phosphatidyl Choline (Lecithin)
   - Phosphatidyl ethanolamine
   - Phosphatidyl serine
   - Phosphatidyl inositol
   - Palmitoyl sphingomyelin
2) Gangliosides found on grey matter.
3) STEROLS: These are the cholesterol or derivatives of cholesterol which are incorporated in liposomes. Examples of Cholesterol derivatives used in the preparation of liposomes include:
   - Cholesterol Hemi Succinate
   - Lysine-based cholesterol
   - PEGylated Cholesterol Neutral [11].

ADVANTAGES

There are numerous medications on the market with good therapeutic activity, but they are only employed in the most reliable situations due to their poor pharmacokinetics and pharmacodynamics. Because the pharmacokinetics and pharmacodynamics of drugs encapsulated in liposomes may be controlled, they can be used on a regular basis. Listed below are some of the liposome's advantages12,13,14:

1. Provides selective passive tumor tissue targeting (Liposomal doxorubicin).
2. Enhancements in efficacy and therapeutic index.
3. Encapsulation of drug thus increased stability.
4. As they have site specific action, so help to decrease hazardous medication exposure to sensitive tissue.
5. Capable of carrying both hydrophilic and hydrophobic drug.
6. Improved pharmacokinetic effects (lower elimination, longer circulation durations).
7. The ability to combine with site-specific ligands to achieve active targeting.
8. Can be formulated into a variety of sizes.

Disadvantages [15,16,17]

1. **High production cost:** One is that they are expensive to make because of the costly material and equipment needed. When it comes to the synthesis of phospholipids, cost is a problem.
2. **Entrapment efficacy:** They have limitations in terms of the amount of drug they carry, which is relatively low. So are not able to hold a large amount of drug within it.

1. **Drug leakage:** There can be instances where the drug may leak out of the liposomes. It's important to consider these factors when using liposomes as a drug delivery system.

2. **Short self-life:** Can affect the effectiveness of a drug delivery system.
3. **Stability:** Due to physical and chemical deterioration, establishing the stability of a liposomal formulation is extremely challenging.

1) BASED ON STRUCTURE

CLASSIFICATION OF LIPOSOMES [18,19]

S. NO	VESICLE TYPE	ABBREVIATION	DIAMETER SIZE	NO. OF LIPID LAYERS
1	Unilamellar vesicle	UV	All size ranges	One
2	Small Unilamellar vesicle	SUV	20-100 nm	One
3	Medium Unilamellar vesicle	MUV	>100 nm	One
4	Large Unilamellar vesicle	LUV	>100 nm	One
5	Giant Unilamellar vesicle	GUV	>1.0 µm	One
6	Oligolamellar vesicle	OLV	0.1-1.0 µm	One
7	Multilamellar vesicle	MLV	> 0.5 µm	5-25
8	Multi vesicular vesicle	MV	> 1.0 µm	Multi compartment structure

2) BASED ON METHOD OF LIPOSOME PREPRATION20

S. NO	PREPRATION METHOD	NO. OF LIPID LAYERS
1	Single or Oligo lamellar vesicle by reverse-phase evaporation method	REV
2	Multi Unilamellar vesicle made by reverse-phase evaporation method	MLV_REV
3	Stable pluri lamellar vesicle	SPLV
4	Frozen and Thawed Multi lamellar vesicle	FATMLV
5	Vesicle prepared by extrusion technique	VET
6	Dehydration-Rehydration method	DRV

3) BASED ON COMPOSITION AND APPLICATION21

S.NO	TYPES OF LIPOSOMES	ABBREVIATION	COMPOSITION
1	Conventional Liposomes	CL	Neutral or negatively charge phospholipids and cholesterol
2	Fusogenic Liposomes	RSVE	Reconstituted sendai virus envelops
3	ph-sensitive Liposomes		Phospholipids such as DOPE or PER with either OA or CHEMS
4	Cationic Liposomes		Cationic lipid with DOPE
5	Long-circulatory(stealth) Liposomes	LCL	Neutral high temp, cholesterol and 5-10% PEG, DSP
6	Immuno Liposomes	IL	CL or LCL with monoclonal antibody linked or sequences of recognition

METHOD OF PREPRATION OF LIPOSOMES

There are several methods for preparing liposomes. The following parameters determine which liposome preparation technique is best: the physicochemical properties of the substance to be entrapped and those of the liposomal ingredients, the type of medium in which the lipid vesicles are dispersed, the effective concentration of the entrapped substance and its potential toxicity, other processes involved during application/delivery of the vesicles22.

It's important to consider these factors as they help to ensure safe and effective liposomal products.

Here we will outline several methods for the preparation of liposomes.

❖ SONICATION

Sonication is probably the most widely used process for preparing SUV. Under a passive atmosphere, MLVs are sonicated with a bath type sonicator or a probe sonicator. However, this method has some drawbacks, like its limited internal volume/encapsulation efficacy, the risk of degrading the phospholipid and compound being encapsulated, metal pollution from the probe tip. Additionally, there may be MLV present alongside SUV23.

There are two sonication techniques:

Probe sonication: The tip of a sonicator is immersed directly in the liposome dispersion. In this approach, the energy input into lipid dispersion is very high. Since the coupling of energy at the tip generates local heat, the vessel must be submerged in a water/ice bath. More than 5% of the lipids can be de-esterified during sonication for up to 1 hour. Titanium will also peel off and contaminate the solution while using the probe sonicator [9].

Bath sonication: It is a method where the liposomes are placed in a cylinder and submerged in a bath sonicator at a controlled temperature. It's usually an easier method in comparison to direct sonication using a probe. The liposomes can be protected in a sterile vessel or under an inert atmosphere during sonication [24].

❖ FRENCH PRESS CELL METHOD

The French Press method converts unstable MLVs to SUVs and LUVs by passing them through a small

orifice of equipment. Liposomes prepared via this method are more reliable because they exhibit better stability than those prepared using the sonication method. The primary drawback of this strategy is that it has a small working volume of no more than 50ml, and a high temperature can be challenging to control [5].

- FREEZE-THAWED LIPOSOMES

  SUVs produced by the sonication method are frozen and thawed slowly and continuously, which leads to the development of LUVs due to SUV aggregation during the thawing phase. Encapsulation efficacies improved by 20%-30% using this approach.[5] This type of synthesis is strongly inhibited by increasing the phospholipid concentration and by increasing the ionic strength of the medium9.

- LIPID FILM HYDRATION BY HANDSHAIKING METHOD

  MLV liposomes can be prepared using this technique. In this method, the lipid is solubilized in an organic solvent basically ethanol in a round bottom flask with continuous circular shaking. As the organic solvent evaporates, a thin lipid film forms on the RBF, which when hydrated with purified water forms a liposome with further continuous circular shaking [11].

- MICRO EMULSIFICATION

  Small lipid vesicles are generated in commercial scales using this method. The instrument known as a micro fluidizer is used to create tiny vesicles from concentrated lipid solution. The lipids should be added to the fluidizer as a suspension of big MLVs. The apparatus pumps fluid through a 5 mm screen under very high pressure.[10] Then, a lengthy microchannel is forced, causing two fluid streams to collide at a straight angle and at a very high speed. By controlling rotation rates between 20 and 200, micro emulsion for biological applications can be created [12].

- MEMBRANE EXTRUSION

  A polymer sieve with a web-like construction which forms a tortuous-path capillary pore, an interconnected network with at least a 100-micron thick membrane, is used for processing a heterogeneous liposomal suspension. The treated liposomes had a narrow size dispersion and a specified mean size of less than 0.4 micron. This method can be used to process LUVs and MLVs18.DRIED RECONSTITUTED VESICLES

  In this method, liposomes are mixed with lyophilized protein or an aqueous solution containing a medication which are then dehydrated/dried out [21].

- Ether Injection

  At 55°C to 65°C or under reduced pressure, a solution of lipids dissolved in diethyl ether or an ether-methanol mixture is progressively added to an aqueous solution of the material that needs to be encapsulated. then there is elimination of ether under vacuum, resulting in production of liposomes. The technique's principal drawbacks are the population's heterogeneity (70 to 200 nm) and the substance that needs to be encapsulated its exposure to organic solvents at high temperatures [23].

- ETHANOL INJECTION (SOLVENT VAPORIZATION)

  This technique is pretty simple. Basically, in this method, an excess of saline or other aqueous media is quickly incorporated with an ethanol lipid solution through a small needle. Ethanol is dissolved in water, and phospholipid molecules spread evenly throughout the liquid. The biggest drawback of this strategy is the possibility of heterogeneous particle sizes (30–110 nm). Another significant drawback is that it is challenging to completely remove all of the ethanol, which could result in the creation of an azeotrope with water [22].

- REVERSE PHASE EVAPORATION

  The lipid mixture is added to round bottom flask and the solvent is removed under pressure by a rotary evaporation. The system is purged with nitrogen and lipids are re-dissolved in the organic phase, vesicles will form. Diethyl ether and isopropyl ether are the usual solvent of choice. After the lipids are re-dissolved the emulsion is obtained and after that the solvent is evaporated from the emulsion by evaporation under reduced pressure resulting in a semisolid gel. Non encapsulated material is then removed, and the liposomes formed are called Reverse phase evaporation vesicles (REV). Large macromolecules can be made using this technique quite effectively [24].

EVALUATION PARAMETERS

For evaluation purposes, the characterization parameters can be divided into three categories: Physical, Chemical, and Biological parameters.[10]

Size, shape, surface, and drug release profile are among the **Physical evaluation parameters**. Investigations to determine the potency and purity of various lipophilic ingredients are included in **Chemical evaluation parameters**. The use of **Biological characterization factors** can help determine a formulation's appropriateness and safety for therapeutic use. Among the parameters are:[10]

Shape and lamellarity of the vesicle: The shape of the vesicle is determined by electron microscopy. Using Freeze Fracture Electron Microscopy and P31 Nuclear Magnetic Resonance Analysis, the lamellarity of the vesicles is determined [10].

Vesicle size and Size distribution: By using photon correlation spectroscopy, the liposome size distribution was identified [10].

Drug encapsulation percentage: The percentage of

drug encapsulation indicates the amount of drug encapsulated or trapped in the liposome vesicle. The percentage of drugs that liposomes encapsulate can be estimated using column chromatography. The drug is both free (unencapsulated) and encapsulated in the formulation. The free drug is removed from the encapsulated drug in order to determine the precise amount of drug encapsulated [4].

Surface Charge: It is crucial to understand the surface charge on the vesicle surface because the charge on the liposome surface has a significant impact on the in vivo distribution. To determine the surface charge of the vesicle, two techniques can be used: zeta potential testing and free-flow electrophoresis [4].

Drug release analysis: The dialysis method is used to analyze the drug release profile of liposomes.[5]

The FDA initially approved a liposomal product in 1995 under the name Doxil (doxorubicin HCl liposome injection). Of these marketed medications, 43% were approved before the year 2000, and 57% were approved prior to the year 2010. The therapeutic field primarily focuses on the treatment of cancer, but it also includes other fields including infection, anesthesia, vaccination, lung disease, and photodynamic therapy. Sterile solution and lyophilized powder are the major dosing forms. Intravenous Infusion, intrathecal and intramuscular injections, epidurals, local infiltrations, and oral inhalations are among the administration methods.12 [12].

RECENT ADVANCEMENTS [11,13]

Ethosomes

They are efficiently organized to deliver the 30% ethanol and soy phosphatidylcholine-based product to the skin.

Immuno liposomes

They are modified by adding antibodies to liposomes. The addition of antibodies enhanced them.

Noisome

Unilamellar vesicles that are small and formed of non-ionic surfactants.

Stealth liposomes

These are brand-new liposome varieties created to increase stability and lengthen their half-life in circulation. These liposomes are prepared using PEG coating.

APPLICATIONS OF LIPOSOMES

The past 30 years have seen a significant advancement in liposome research. Today, a wide range of liposomes with different sizes, phospholipid compositions, cholesterol compositions, and surface morphologies may be created that are suited for a number of applications. The liposome carrier may be used to target the liver and spleen, and tomography can easily distinguish between malignant and non-malignant tissue [11].

Liposome for Respiratory Drug Delivery System

Typically, liposomes are utilized to treat various respiratory problems. There are now many injectable liposome-based medications on the market, including Ambisome, Fungisome, and Myocet. The effectiveness of the liposomal drug delivery mechanism to the lungs depends on the lipid composition, charge, size, drug & lipid ratio, and administration methods [11].

Liposome as Vaccine Adjuvant

Liposomes are known as an immune adjuvant that improves both cell-mediated and non-cell-mediated immunity is liposomes. After being injected intramuscularly, liposomal immune adjuvants slowly and passively release encapsulated antigen into the targeted lymph node [11].

Liposome as Anti-Infective Agents

The liver and spleen are habitat to intracellular pathogen such protozoa, bacteria, and fungi; hence, medicinal compounds can be supplied to such organs using liposomes as the transport method to remove these pathogens. By combining and directing the treatment with the liposomal carrier, disorders like leishmaniasis, histoplasmosis, candidiasis, erythrococosis, aspergelosis, gerardiasis, TB, and malaria can be treated [11].

Table 1: Available products in market.

BRAND NAME	DRUG	DOSAGE FORM	ADM. ROUTE	INDICATION
Ambisome	Amphotericin B	Lyo	IV	Fungal Infection
Abraxane	Paclitaxel	Suspension	IV	Breast Cancer, Lung cancer
Annamycin	Annamycin	-	-	Breast Cancer, Leukemia
ATRAGEN	All-transretionic acid	-	-	Prostate Cancer, Leukemia
Arikayce	Amikacin sulfate	Suspension	Oral inhalation	Lung's disease
Daouno Xome	Daunorubicin	Suspension	IV	Kaposi Sarcoma
Doxil	Doxorubicin	Suspension	IV	Refractory Kaposi's sarcoma, recurrent breast cancer, and ovarian cancer
DepoDur	Morphine	Suspension	Epidural	Analgesic
DepoCyt	Cytarabine	Suspension	IT	Neoplastic meningitis and lymphomatous meningitis
Exparel	Bupivacaine	Suspension	Local infiltration	Analgesic
Fungisome	Amphotericin B	-	-	Anti-Fungal
Lipoplatin	Cisplatin	-	-	Epithelial malignancies
Lipusu	Paclitaxel	-	-	Breast Cancer, Lung cancer
Marqibo	Vincristine Sulfate	3 vials	IV	Leukemia
Myocet	Doxorubicin	3 vials	IV	Recurrent breast cancer
Mepact	Mefamurtide	Lyo	IV	Osteosarcoma
Nyotran	Nystatin			Fungal infection
Onivyde	Irinotecan hydrochloride trihydrate	Suspension	IV	Pancreatic adenocarcinoma
Visudyne	Verteporfin	Lyo	IV	Age-related macular degeneration, pathological myopia, and ocular histoplasmosis
Vyxeos	Daunorubicin, cytarabine	Lyo	IV	Leukemia

Liposome in the Treatment of Tumor Cells

When administered for a long time, anti-cancer medications have dangerous side effects that can be very significant. By minimizing side effects, liposomal therapy for tumor cell targeting has improved the area of cancer treatment.[11]

Uses in Cosmetics

The characteristics of liposomes are also used in the delivery of cosmetics ingredients. Liposomes have benefits as lipids stay hydrated and prevent skin dryness, which is a major factor in ageing. In 1986, Christian Dior introduced Capture, an anti-aging lotion, as the first liposomal cosmetic product to hit the market[25].

FUTURE PROSPECTIVE OF LIPOSOMES

Future medical liposomal applications could allow us

to transform innovative medications into both conventional and improved-circulation liposomes. It is also promising for delivering ribozymes and oligonucleotides (anti-sense). The other areas include targeted medication delivery, diagnostic tests, and immunotherapy, in which the researcher's strategy for further development or advancement. Numerous other businesses, including those in the food, cosmetic, nutrition, and coating industries, are further areas of liposomal development. Since liposomes are made of pricey raw materials, there is a demand for less expensive liposomes. In the future, liposomes may have a significant impact in the sectors of agriculture and ecology.

Conclusion

The analysis led to the conclusion that liposomes are highly effective as a drug delivery system. Both hydrophilic and lipophilic drugs are easily encapsulated in liposomes. The drug was administered to the patient in a regulated manner or was targeted for a particular location. The liposomal technique can be employed to improve pharmacokinetics and therapeutic impact while reducing adverse effects.

Liposomes have been effectively used for treating a variety of illnesses, from cancer to pain management. Several formulations of liposomes are currently available on the market.medications can be used. A suitable method for achieving the therapeutic activity of such medicines is liposome formulation. Because it is inert and resembles a cellular membrane, liposome construction has improved its dependability, making it an exciting area for scientific investigation. A liposome is an effective drug delivery system for chemotherapy and is used in the treatment of cancer.[5]

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