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**Review Article**

# A Comprehensive Review on Preparation Methods, Importance and Future Prospect of Liposomes

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**Abstract:**

Liposomes are uni-/multilamellar phospholipid vesicles composed of concentric spherical layers of aqueous zones sandwiched between phospholipid membranes. Both water and oil soluble drugs can be encapsulated in the liposomes either in the aqueous zone or the lipid-bilayers according to their solubility. The aim of NDDS is to provide a therapeutic amount of drug to the appropriate site in the body to accomplish promptly and then maintain the desired drug concentration. The application of liposomes to assist drug delivery has already had a major impact on many biomedical areas. Understanding the advances in liposomal technology to date and the challenges that still need to be overcome, will allow future research to improve on existing platforms and to address the current translational and regulatory limitations. Advances in liposome design are leading to new applications for the delivery of new biotechnology products, for example antisense oligonucleotides, cloned genes, and recombinant proteins. New drug delivery systems have been developed or are being developed to overcome the limitation of the conventional drug delivery systems to meet the need of the healthcare profession. The unique feature of liposomes is that they are biocompatible and biodegradable lipids, and are inert and non-immunogenic.

**Keywords:** NDDS, Regulatory Limitations, Oligonucleotides, Recombinant Proteins, Non-Immunogenic.

## Introduction

### Novel Drug Delivery System

Novel Drug Delivery system (NDDS) refers to the approaches, formulations, technologies, and systems for transporting a pharmaceutical compound in the body as needed to safely achieve its desired therapeutic effects. NDDS is a system for deliveryof drug other than conventional drug delivery system. NDDS is a combination of advance technique and dosage form which are far better than conventional dosage

form[1]. The aim of NDDS is to provide a therapeutic amount of drug to the appropriate site in the body to accomplish promptly and then maintain the desired drug concentration[2]. NDDS combining polymer science, pharmaceutics and molecular biology[3].

Among medicine carriers one can name answerable polymers, microparticles made of undoable or biodegradable, natural and synthetic polymers, microcapsules, cells, cell ghosts, lipoproteins, liposomes, and micelles. The carriers are frequently made sluggish. The degradable, stimulireactive (e.g., pH-or temperature-sensitive), and indeed targeted (e.g., by conjugating them with specific antibodies against certain characteristic factors of the area of interest).

Targeting is the capability to direct the medicine- loaded system to the position of interest.

Two major mechanism be distinguished for addressing the desired site for drug release.

(i) Passive targeting
(ii) Active targeting

An illustration of unresistant targeting is the preferential accumulation of chemotherapeutic agents in solid Excrescences as a result of the enhanced vascular permeability of tumor tissue compared with healthy tissue. A strategy that could allow active targeting involves the face functionalization of drug carriers with ligands that are widely honored by tumor receptors on the face of the cells of interest. Since ligand – receptor relations can be largely picky, this could allow a more precise targeting of the point of interest. Any medicine delivery system may be defined as a system comprising of :

a) Medicine expression
b) Medical device or lozenge form/ technology to carry the medicine inside the body
c) Medium for the release

Conventional medicine delivery involves the expression of the medicine into a suitable form, similar as a compressed tablet for oral administration or a result for intravenous administration.

These lozenge forms have been plant to have serious limitations in terms of advanced lozenge needed, lower effectiveness, toxin and adverse side goods. New drug delivery systems have been developed or are being developed to overcome the limitation of the conventional drug delivery systems to meet the need of the healthcare profession. These systems can be characterized as controlled drug release systems and targeted medicine delivery systems.

The therapeutic benefits of these new systems include

- Increased efficacity of the medicine
- Point specific delivery
- Dropped toxin/ side goods
- Increased convenience
- Feasible treatments for preliminarily incorrigible conditions
- Implicit for precautionary operations
- More patient compliance.

**Current Status and Future Prospects of New Drug Delivery System**

With the progress in all spheres of science and technology, the dosage forms have evolved from simple mixtures and pills to the highly sophisticated technology intensive drug delivery systems, which are known as Novel Drug Delivery Systems (NDDS). Quest for New Drug Delivery System (NDDS) has got new impetus since early eighties to have improved therapeutic outcome from the same drug, because the NDDS have several advantages over the conventional dosage form. Since then several NDDS have been developed and it constitute a sizable portion of the global market.

**Types of Novel Drug Delivery Systems**

There are multiple schemes of classification of types and techniques of NDDS - based on therapeutic group of drugs loaded, physical form, intended application route, mechanism of delivery or action, etc. and none would be complete.

**Microparticulate Drug Delivery Systems**

Drugs encapsulated within polymeric beads in order to control the release, mask taste, prevent degradation from atmospheric moisture and to ensure proper delivery as desired. These multi-unit dosage forms are mainly intended for oral delivery, though parenteral and other routes of administration have also found commercial and clinical success. Different systems implement various rate controlling mechanism including nonerodible mechanical barrier for diffusion controlled release, microporous membrane systems, water swellable and hydrogel systems, pH sensitive polymer coated systems, gastric floatation systems, mucoadhesive systems, colon-specific delivery systems, etc. a large spectrum of drug have been modulated for release and other properties, e.g. cardiovascular drugs, antipsychotics, antibacterial and chemotherapeutic agents. The selection of polymer for a particular multiparticulate system is crucial and a wide variety of polymers such as cellulose derivatives (methyl, ethyl, hydroxypropyl, hydroxypropyl methyl cellulose), acrylic polymers, biodegradable polymers (Polylactide coglycollic acid, poly lactic acid, polyglycollic acid, etc.) and natural polymers (sodium alginate, albumin, other proteins, chitosan, etc.) are used depending on the requirement of the particular system to be developed [4-8].

**Nanoparticles**

These are colloidal drug delivery systems in the nanometer size range having wide application potential at present. They have got all characteristics of the liposomes minus the stability problems. They have been utilized to deliver and control the release of drug molecules from suitable polymeric nanoparticles/ nanospheres. Usually FDA approved biocompatible polymers such as poly (L-lactide - D-glycollic acid) have been used, though other polymers such as polyepsilon-caprolactone, chitosan and polyalkyl cyanoacrylates have been also used. Their most promising area of application is tumor targeting capability. Nanoparticles are not only suitable for parenteral administration, but also they have been exploited as advanced systems for drug delivery through cornea, skin, bronchioles and oral routes.

**Aquasome**

These are carbohydrate stabilized nanoparticles of ceramics / calcium phosphate having water-like properties that help to protect and preserve the fragile biological molecules. They are comprised of a solid nano-crystalline core coated with oligomeric film to which the drug moieties or biochemically active molecules are adsorbed with or without modification. There three layered structures are self-assembled by non-covalent and ionic bonds. Their intended route of administration is parenteral and with advancement of research in this field, other routes might be contemplated [9-11].

**Dendrimers**

In search for novel biomaterials for controlled and targeted delivery of bioactives, StarburstDendrimers are the latest stars that bear promising properties for the delivery of drugs, vaccine, metals or genes to the desired sites. In spite of being polymers they bear similarity with vesicular structures such as micelles, liposomes and globular proteins. The dendrimers are three-dimensional branched structures like trees

and hence the name "Dendrimer". They possess a very large number of chain ends and synthesized chemically. Into the branches of dendrimers drugs and other biologically active molecules could be entrapped for controlled and/or targeted delivery initially via parenteral route and subsequently other routes could be tried.

**Microemulsions**

Microemulsions are transparent thermodynamically stable systems of colloidal nature that are formed from classical emulsions, but at specific phase-volume ratios. They afford solubilization of water-insoluble molecules, thereby improving their bioavailability as well as applicability and reduced ADME problems. A widely used immunosuppressant, Cyclosporin, have been formulated commercially as a microemulsion for increased solubility and bioavailability. Proteins and peptides may also be formulated as oral microemulsions, such as oral insulin systems, and also scope exists in developing oral vaccines through this system.

**Liposomes**

These are uni-/multilamellar phospholipid vesicles composed of concentric spherical layers of aqueous zones sandwiched between phospholipid membranes. Both water and oil soluble drugs can be encapsulated in the liposomes either in the aqueous zone or the lipid-bilayers according to their solubility. They are often referred to as "artificial cells" as they resemble one in almost all practical aspects. They showed immense potential in delivery of anti-tumor therapeutics as well as anti-fungals. Drugs such as Amphotericin B, Doxorubicin and Daunorubicin have been successfully launched in market as liposomes [12-15].

**Niosomes**

These are vesicles like liposomes, but made up of nonionic surfactants and like liposomes. They can also entrap hydrophilic as well as lipophilic drugs. They have better stability than liposomes and hence have greater interest for industrial adoption. The non-ionic surfactant systems make niosomes inherently target-specific to tumor, liver and brain. They have been reported to be useful as targeting systems of drugs for treatment of cancer and in therapy of microbial diseases caused particularly by virus and parasites. Tumor targeting of Methotrexate in mice model have been highly successful. Since no special handling / storage precautions are required for niosomes, their commercial exploitation would be easier. They are biodegradable and reduce systemic toxicity of various antitumor and antimicrobial agents by localizing the drug to specific sites of action.

**Various Drug Delivery Systems**

- Carrier based Drug Delivery System:

A) Liposomes
B) Nanoparticles
C) Microspheres
D) Monoclonal antibodies
E) Niosomes
F) Resealed erythrocytes as Drug carriers

- Trasdermal Drug Delivery Systems:

A) Sonophoresis
B) Mucoadhesive delivery systems
C) Supramolecular delivery systems
D) Variable release delivery systems

**Advantages of novel drug delivery system**[4,5]:

- Optimum dose at the right time and right location
- Efficient use of expensive drugs, excipients and reduction in production cost
- Improves the therapy by increasing the

duration of action and reducing the side effects.
- Increase the patient compliance and provide convenient route of administration.
- Achieve the targeting of drugs to a specific sites which reduces the unwanted side effects and obtain maximum efficacy.
- Reduces the dose and thus reduces the side effects of drugs.

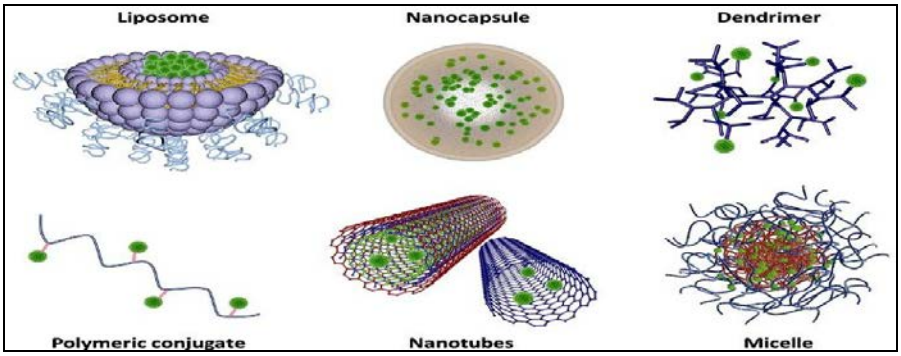


**Figure 1: Different novel drug delivery carrier**

**Merits of TDDS**[4,5]

- Targeting of the drug molecule towards the tissue or organ reduces the toxicity to the normal tissues.
- Increased bioavailability.
- Improved treatment of chronic illness where symptoms break through occurs when the plasma level of the drug falls below the MEC.
- The drug is protected from first pass metabolism and GI degradation.
- Improved patient compliance can be achieved due to decrease in amount and frequency of doses administered.
- Biocompatibility can be well achieved.
- Maintenance of therapeutic action of the drug overnight.
- Systemic and local side effects are successfully reduced due to the reduction in the total amount of the drug.

**Limitations of TDDS**[4,5]

- TDDS such as liposomes, resealed erythrocytes and platelets suffer serious stability problems.
- Though monoclonal antibodies show very high degree of site specificity the selection and isolation procedures are too tough.
- If the particle size of TDDS is high then they may be rapidly cleared by RES.
- Magnetically controlled TDDS shows high specificity to superficially located organs and tissues but cannot be targeted to deep seated organs.
- Monoclonal antibodies may sometimes can cause unwanted antigen – antibody reaction which leads to serious consequences.
- Microspheres of particle size more than 50µg can lead to problem of thrombo-embolism in general circulation.
- Once drug is administered it cannot be removed if an undesirable action is precipitated or if the drug is no longer needed.
- Most of such systems are administered by subcutaneous or intraperitoneal route.
- The vehicles polymer employed should be sterile, hydrogen free, non-irritating,

biocompatible and biodegradable into non-toxic compounds within an appropriate time preferably close to duration of action.

- Drugs having biological half-life of 1hr or less are difficult to formulate as controlled release formulation. The high rates of elimination of such drugs from the body need an extremely large maintenance dose which provides 8 – 12 hrs of continuous therapy [16-18].

**Liposomes- An Introduction**

Liposomes are colloidal, vesicular structure composed of one or more bilayers surrounding an equal number of aqueous compartment[7]. Liposomes are small artificial vesicles of spherical shape that can be created from cholesterol and natural nontoxic phospholipids.

Due to their size and hydrophobic and hydrophilic character (besides biocompatibility), liposomes are promising systems for drug delivery[8]. The sphere like shell encapsulated a liquid interior which contain substances such as peptides, protein, hormones, enzymes, antibiotics, anti-fungal and anti-cancer agents[7].

Liposome properties differ considerably with lipid composition, surface charge, size, and the method of preparation.

Furthermore, the choice of bilayer components determines the 'rigidity' or 'fluidity' and the charge of the bilayer.

For instance, unsaturated phosphatidylcholine species from natural sources (egg or soybeanphosphatidylcholine) give much more permeable and less stable bilayers, whereas the saturated phospholipids with long acyl chains (for example, dipalmitoylphosphatidylcholine) form a rigid, rather impermeable bilayer structure[8].

It has been displayed that phospholipids impulsively form closed structures when they are hydrated in aqueous solutions. Such vesicles which have one or more phospholipid bilayer membranes can transport aqueous or lipid drugs, depending on thenature of those drugs. Because lipids are amphipathic (both hydrophobic and hydrophilic) in aqueous media, their thermodynamic phase properties and self-assembling characteristics influence entropically focused confiscation of their hydrophobic sections into spherical bilayers. Those layers are referred to as lamellae[9].

Liposomes particle sizes ranges from 30 nm to several micrometers. They consist of one or more lipid bilayer surrounding aqueous units, where the polar head groups are oriented in the pathway of the interior and exterior aqueous phases.

On the other hand, self-aggregation of polar lipids is not limited to conventional bilayer structures which rely on molecular shape, temperature, and environmental and preparation conditions but may self-assemble into various types of colloidal particles[10].

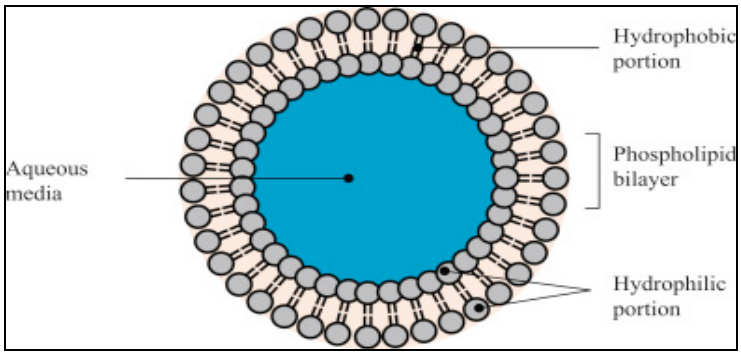


**Figure 2: Structure of liposome**

**Methods of liposome preparation**

**General methods of preparation**

All the methods of preparing the liposomes involve four basic stages:
1. Drying down lipids from organic solvent.
2. Dispersing the lipid in aqueous media.
3. Purifying the resultant liposome.
4. Analysing the final product.

**Method of liposome preparation and drug loading**

The following methods are used for the preparation of liposome:
1. Passive loading techniques
2. Active loading technique.

**Passive loading techniques include three different methods:**
1. Mechanical dispersion method.
2. Solvent dispersion method.
3. Detergent removal method (removal of non-encapsulated material)

**1. Mechanical dispersion method**

The following are types of mechanical dispersion methods:
1.1. Sonication.
1.2. French pressure cell: extrusion.
1.3. Freeze-thawed liposomes.
1.4. Lipid film hydration by hand shaking, non-hand shaking or freeze drying.
1.5. Micro-emulsification.
1.6. Membrane extrusion.

**1.1. Sonication:** Sonication is perhaps the most extensively used method for the preparation of SUV. Here, MLVs are sonicated either with a bath type sonicator or a probe sonicator under a passive atmosphere. The main disadvantages of this method are very low internal volume/encapsulation efficacy, possible degradation of phospholipids and compounds to be encapsulated, elimination of large molecules, metal pollution from probe tip, and presence of MLV along with SUV [20-22].

There are two sonication techniques:

**a) Probe sonication:** The tip of a sonicator is directly engrossed into the liposome dispersion. The energy input into lipid dispersion is very high in this method. The coupling of energy at the tip results in local hotness; therefore, the vessel must be engrossed into a water/ice bath. Throughout the sonication up to 1 h, more than 5% of the lipids can be deesterified. Also, with the probe sonicator, titanium will slough off and pollute the solution.

**b) Bath sonication:** The liposome dispersion in a cylinder is placed into a bath sonicator. Controlling the temperature of the lipid dispersion is usually easier in this method, in contrast to sonication by dispersal directly using the tip. The material being sonicated can be protected in a sterile vessel, dissimilar the probe units, or under an inert atmosphere.

**1.2. French pressure cell:** extrusion French pressure cell involves the extrusion of MLV through a small orifice. An important feature of the French press vesicle method is that the proteins do not seem to be significantly pretentious during the procedure as they are in sonication. An interesting comment is that French press vesicle appears to recall entrapped solutes significantly longer than SUVs do, produced by sonication or detergent removal.

The method involves gentle handling of unstable materials. The method has several advantages over sonication method. The resulting liposomes are rather larger than sonicated SUVs. The drawbacks of the method are that the high temperature is difficult to attain, and the working volumes are comparatively small (about 50 mL as the maximum) [23-26].

**1.3. Freeze-thawed liposomes** SUVs are rapidly frozen and thawed slowly. The short-lived sonication disperses aggregated

materials to LUV. The creation of unilamellar vesicles is as a result of the fusion of SUV throughout the processes of freezing and thawing. This type of synthesis is strongly inhibited by increasing the phospholipid concentration and by increasing the ionic strength of the medium. The encapsulation efficacies from 20% to 30% were obtained.

**2. Solvent dispersion method**

**Ether injection (solvent vaporization):** A solution of lipids dissolved in diethyl ether or ether-methanol mixture is gradually injected to an aqueous solution of the material to be encapsulated at 55°C to 65°C or under reduced pressure. The consequent removal of ether under vacuum leads to the creation of liposomes. The main disadvantages of the technique are that the population is heterogeneous (70 to 200 nm) and the exposure of compounds to be encapsulated to organic solvents at high temperature [27-29].

**Ethanol injection:** A lipid solution of ethanol is rapidly injected to a huge excess of buffer. The MLVs are at once formed. The disadvantages of the method are that the population is heterogeneous (30 to 110 nm), liposomes are very dilute, the removal all ethanol is difficult because it forms into azeotrope with water, and the probability of the various biologically active macromolecules to inactivate in the presence o f even low amounts of ethanol is high.

**Reverse phase evaporation method:** This method provided a progress in liposome technology , since it allowed for the first time the preparation of liposomes with a high aqueous space-to-lipid ratio and a capability to entrap a large percentage of the aqueous materialpresented. Reverse-phase evaporation is based on the creation of inverted micelles. These inverted micelles are shaped upon sonication of a mixture of a buffered aqueous phase, which contains the water-soluble molecules to be encapsulated into the liposomes and an organicphase in which the amphiphilic molecules are solubilized. The slow elimination of the organic solvent leads to the conversion of these inverted micelles into viscous state and gel form. At a critical point in this process, the gel state collapses, and some of the inverted micelles were disturbed. The excess of phospholipids in the environment donates to the formation of a complete bilayer around the residual micelles, which results in the creation of liposomes. Liposomes made by reverse phase evaporation method can be made from numerous lipidformulations and have aqueous volume-to-lipid ratios that are four times higher than hand-shaken liposomes or multilamellar liposomes.

Briefly, first, the water-in-oil emulsion is shaped by brief sonication of a two-phase system, containing phospholipids in organic solvent such as isopropyl ether or diethyl ether or a mixture of isopropyl ether and chloroform with aqueous buffer. The organic solvents are detached under reduced pressure, resulting in the creation of a viscous gel. The liposomes are shapedwhen residual solvent is detached during continued rotary evaporation under reduced pressure. With this method, high encapsulation efficiency up to 65% can be obtained in a medium of low ionic strength for example 0.01 M NaCl. The method has been used to encapsulatesmall, large, and macromolecules. The main drawback of the technique is the contact of the materials to be encapsulated to organic solvents and to brief periods of sonication. These conditions may possibly result in the breakage of DNA strands or the denaturation of someproteins. Modified reverse phase evaporation method was presented by Handa et al., and the main benefit of the method is that the liposomes had high encapsulation efficiency (about 80%) [30-32].

**Detergent removal method (removal of non-encapsulated material)**

**Dialysis** The detergents at their critical micelle concentrations (CMC) have been used to solubilize lipids. As the detergent is detached, the micelles become increasingly better-off in phospholipid and lastly combine to form LUVs. The detergents were removed by dialysis. A commercial device called LipoPrep (Diachema AG, Switzerland), which is a version of

dialysis system, is obtainable for the elimination of detergents. The dialysis can be performed in dialysis bags engrossed in large detergent free buffers (equilibrium dialysis) [17].

**3. Detergent (cholate, alkyl glycoside, Triton X-100) removal of mixed micelles (absorption)** Detergent absorption is attained by shaking mixed micelle solution with beaded organic polystyrene adsorbers such as XAD-2 beads (SERVA Electrophoresis GmbH, Heidelberg, Germany) and Bio-beads SM2 (Bio-Rad Laboratories, Inc., Hercules, USA). The great benefit of using detergent adsorbers is that they can eliminate detergents with a very low CMC, which are not entirely depleted.

**Gel-permeation chromatography** In this method, the detergent is depleted by size special chromatography. Sephadex G-50, Sephadex G-l 00 (Sigma-Aldrich, MO,USA), Sepharose 2B-6B, and Sephacryl S200-S1000 (General Electric Company, Tehran, Iran) can be used for gel filtration. The liposomes do not penetrate into the pores of the beads packed in a column. They percolate through the inter-bead spaces. At slow flow rates, the separation of liposomes from detergent monomers is very good. The swollen polysaccharide beads adsorb substantial amounts of amphiphilic lipids; therefore, pre-treatment is necessary. The pre-treatment is done by pre-saturation of the gel filtration column by lipids using empty liposome suspensions.

**Drug loading in liposomes:**

Drug loading can be attained either passively (i.e., the drug is encapsulated during liposome formation) or actively (i.e., after liposome formation). Hydrophobic drugs , for example amphotericin B taxol or annamycin, can be directly combined into liposomes during vesicle formation, and the amount of uptake and retention is governed by drug-lipid interactions. Trapping effectiveness of 100% is often achievable, but this is dependent on the solubility of the drug in the liposome membrane [33-35].

Passive encapsulation of water-soluble drugs depends on the ability of liposomes to trap aqueous buffer containing a dissolved drug during vesicle formation.

Trapping effectiveness (generally <30%) is limited by the trapped volume delimited in the liposomes and drug solubility. On the other hand, water-soluble drugs that have protonizable amine functions can be actively entrapped by employing pH gradients, which can result in trapping effectiveness approaching 100%.

**Freeze-protectant for liposomes (lyophilization):** Natural excerpts are usually degraded because of oxidation and other chemical reactions before they are delivered to the target site. Freeze-drying has been a standard practice employed to the production of many pharmaceutical products. The overwhelming majority of these products are lyophilized from simple aqueous solutions. Classically, water is the only solvent that must be detached from the solution using the freeze-drying process, but there are still many examples where pharmaceutical products are manufactured via a process that requires freeze-drying from organic co-solvent systems [36-39].

Freeze-drying (lyophilization) involves the removal of water from products in the frozen state at tremendously low pressures. The process is normally used to dry products that are thermo-labile and would be demolished by heat-drying. The technique has too much potential as a method to solve long-term stability difficulties with admiration to liposomal stability. Studies showed that leakage of entrapped materials may take place during the process of freeze-drying and on reconstitution. Newly, it was shown that liposomes when freeze-dried in the presence of adequate amounts of trehalose (a carbohydrate commonly found at high concentrations in organism) retained as much as 100% of their original substances. It shows that trehalose is an excellent cryoprotectant (freeze-protectant) for liposomes. Freeze-driers range in size from small laboratory models to large industrial units available from pharmaceutical equipment supplies [40-42].

**Mechanism of transportation through liposome:**

The limitations and benefits of liposome drug carriers lie critically on the interaction of liposomes with cells and their destiny in vivo after administration. In vivo and in vitro studies of the contacts with cells have shown that the main interaction of liposomes with cells is either simple adsorption (by specific interactions with cell-surface components, electrostatic forces, or by non-specific weak hydrophobic) or following endocytosis (by phagocytic cells of the reticuloendothelial system, for example macrophages and neutrophils).

Fusion with the plasma cell membrane by insertion of the lipid bilayer of the liposome into the plasma membrane, with simultaneous release of liposomal content into the cytoplasm, is much rare. The fourth possible interaction is the exchange of bilayer components, for instance cholesterol, lipids, and membrane-bound molecules with components of cell membranes. It is often difficult to determine what mechanism is functioning, and more than one may function at the same time.

**Applications of liposomes in medicine and pharmacology**

Applications of liposomes in medicine and pharmacology can be divided into diagnostic and therapeutic applications of liposomes containing various markers or drugs , and their use as a tool, a model, or reagent in the basic studies of cell interactions, recognition processes,and mode of action of certain substances. Unfortunately, many drugs have a very narrow therapeutic window, meaning that the therapeutic concentration is not much lower than the toxic one. In several cases, the toxicity can be reduced or the efficacy can be enhanced by the use of a suitable drug carrier which alters the temporal and spatial delivery of the drug, i.e.,its biodistribution and pharmacokinetics. It is clear from many pre-clinical and clinical studies that drugs, for instance antitumor drugs, parceled in liposome demonstration reduced toxicities, while retentive enhanced efficacy [43-45].

Advances in liposome design are leading to new applications for the delivery of new biotechnology products, for example antisense oligonucleotides, cloned genes, and recombinant proteins. A vast literature define the viability of formulating wide range of conservative drugs in liposomes, frequently resultant in improved therapeutic activity and/or reduced toxicity compared with the free drug. As a whole, changed pharmacokinetics for liposomal drugs can lead to improved drug bioavailability to particular target cells that live in the circulation, or more prominently, to extravascular disease sites, for example, tumors. Recent improvements include liposomal formulations of all-trans-retinoic

acid and daunorubicin, which has received. Food and Drug Administration consent as a first-line treatment of AIDS-related advanced Kaposi's sarcoma. Distinguished examples are vincristine, doxorubicin, and amphotericin B.

The benefits of drug load in liposomes , which can be applied as (colloidal) solution, aerosol, or in (semi) solid forms , such as creams and gels, can be summarized into seven categories (Table 1):

**Table 1: Benefits of drug load in liposomes**

| S.no | Benefits of drug load in liposome | Examples |
|---|---|---|
| 1. | Improved solubility of lipophilic and amphiphilic drugs. | Amphotericin B, porphyrins, minoxidil, some peptides, and anthracyclines, respectively; hydrophilic drugs, such as anticancer agent doxorubicin or acyclovir. |
| 2. | Passive targeting to the cells of the immune system, especially cells of the mononuclear phagocytic system. | Antimonials, amphotericin B, porphyrins, vaccines, immunomodulators. |
| 3. | Sustained release system of systemically or locally administered liposome. | Doxorubicin, cytosine arabinoside, cortisones, biological proteins or peptides such as vasopressin. |
| 4. | Site-avoidance mechanism. | Doxorubicin andamphotericin B . |
| 5. | Site-specific targeting. | Anti-inflammatory drugs, anti-cancer, anti-infection. |
| 6. | Improved transfer of hydrophilic, charged molecules. | Antibiotics, chelators, plasmids, and genes. |
| 7. | Improved penetration into tissue. | Corticosteroids, anesthetics, and insulin. |

**Advantages of Liposomes:**

Some of the advantages of liposome are as follows:

1) It can carry both water and lipid soluble drugs.
2) Provides selective passive targeting to tumor tissues (liposomal doxorubicin).
3) Liposome increased stability via encapsulation.
4) Liposomes are non-toxic, flexible, biocompatible, completely biodegradable, and non-immunogenic for systemic and non-systemic administrations.
5) Liposomes reduce the toxicity of the encapsulated agent (amphotericin B, Taxol).
6) Liposomes help reduce the exposure of sensitive tissues to toxic drugs.
7) Site avoidance effect.
8) Flexibility to couple with site-specific ligands to achieve active targeting.
9) Improved pharmacokinetic effects (reduced elimination, increased circulation lifetimes).
10) It provides sustained release.
11) It can be administered through various routes.
12) It engenders incorporate micro and macro molecules.
13) It also acts as reservoir of drugs.
14) Liposomes can modulate the distribution of drug.
15) Its direct interaction of the drug with cell.

**Disadvantages of Liposomes:**

**1)** Low solubility.
**2)** Sometimes phospholipid undergoes oxidation and hydrolysis-like reaction.
**3)** Short half-life.

**4)** Leakage and fusion of encapsulated drug/molecules.
**5)** Production cost is high.
**6)** Fewer stables.
**7)** Quick uptake by cells of reticuloendothelial system (R.E.S).
**8)** Allergic reactions may occur to liposomal constituents.
**9)** Problem to targeting to various tissues due to their large size.

**Importance of the study**

Liposomes have been extensively used in the treatment of several diseases. Liposomes improve the therapeutic efficacy by enhancing drug absorption while avoiding or minimizing rapid degradation and side effects, prolonging the biological half-life and reducing toxicity.
The unique feature of liposomes is that they are biocompatible and biodegradable lipids, and are inert and non-immunogenic.
Liposomes can compartmentalize and solubilize both hydrophilic and hydrophobic materials. All these properties of liposomes and their flexibility for surface modification to add targeting moieties make liposomes more attractive candidates for use as drug delivery vehicles.
There are many novel liposomal formulations that are in various stages of development, to enhance therapeutic effectiveness of new and established drugs [47-52].

**Significance of the study**

Liposomes are among the first nanomolecular drug delivery systems to demonstrate the increased delivery of small molecular weight anticancer drugs to solid tumors by altering the biodistribution of associated drugs.
To improve the efficacy of drug by targeted drug delivery in order to reduces toxicity metastasis of colorectal cancer, increase bioavailability, blood circulation time since PEG decreases the recognition of liposomes by the mononuclear phagocyte system thereby exhibiting prolong half-life.
Mostly reduced peripheral neuropathy of anticancer formulation by adding glutathione like antioxidant agent in there preparation.
Liposomes as a novel type of drug carrier,

- Exhibit good targeting properties
- Slow releasing potential
- High stability (freeze dried)
- Low toxicity with surface modification.

**Summary**

The application of liposomes to assist drug delivery has already had a major impact on many biomedical areas. Understanding the advances in liposomal technology to date and the challenges that still need to be overcome, will allow future research to improve on existing platforms and to address the current translational and regulatory limitations. New drug delivery systems have been developed or are being developed to overcome the limitation of the conventional drug delivery systems to meet the need of the healthcare profession. Continued translational success will require communication and collaboration between experts involved in all stages of pharmaceutical development of liposomal technologies, including manufacturing and pharmaceutical design, cellular interactions and toxicology, as well as preclinical and clinical evaluation.

**References**

**1.** Tariq Jamshaid. Pharmaceutics & novel drug delivery systems. Pharmaceutical regulatory affairs, 2015; 4(3):74.
**2.** Kalra1, N. and G. Jeyabalan. Niosomes: a versatile drug delivery system. Research journal of life sciences, bio-informatics, pharmaceutical and chemical science, 2016; 2(4): 44-54.

**3.** Nagashree, K. Novel drug delivery system. Research & Reviews: Journal of Pharmaceutics and Nanotechnology, 2015; 3(2): 32-36.

**4.** https://www.uniassignment.com/essay-samples/biology/advantages-of-novel-drug-delivery-systems-biology essay .php

**5.** Patil, S., Mhaiskar, A. and Mundhada, D. A review on novel drug delivery system: a recent trend. International Journal of Current Pharmaceutical & Clinical Research, 2016; 6(2): 89-93.

**6.** R.R. Bhagwat and I.S. Vaidhya. Novel drug delivery systems: An overview. International journal of pharmaceutical sciences and research, 2013; 4(3): 970-982.

**7.** Kant, S., Kumar, S. and Prashar, B. A complete review on: Liposomes. International research journal of pharmacy, 2012; 3(7):10-16.

**8.** Abolfazl, A., Rezaei-Sadabady, R., Davaran, S., Sang Woo Joo, Zarghami, N., Hanifehpour, Y., Mohammad, S., Mohammad, K. and Kazem, N.K.,. Liposome: classification, preparation, and applications. Nanoscale Research Letters, 2013; 8(102):1-9

**9.** S. Suggy Chrai, R. Murari, and Imran Ahmad. Liposomes: A Review. Biotech Trends, 2001; 14(11):10–14.

**10.** W Andreas, Karola-Uhl. Liposome technology for industrial purposes. Journal of Drug Delivery; 2011:1-9

**11.** Salari, N., Mansouri, K., Valipour, E. et al. (2021) Hyaluronic acid-based drug nanocarriers as a novel drug delivery system for cancer chemotherapy: A systematic review. DARU J Pharm Sci https://doi.org/10.1007/s40199-021-00416-6

**12.** Kumar, Inder, Dhiman, S., Palia, P., Kumar, P., and Sharma, N., et al. (2021). "Dendrimers: Potential Drug Carrier For Novel Drug Delivery System". Asian Journal of Pharmaceutical Research and Development 9 (2), 70-79. https://doi.org/https://doi.org/10.22270/ajprd.v9i2.945.

**13.** Bhosale, R.R., Gangadharappa, H.V., Osmani, R.A.M. et al. (2020). Design and development of polymethyl methacrylate-grafted gellan gum (PMMA-g-GG)-based pH-sensitive novel drug delivery system for antidiabetic therapy. Drug Delivery. and Transl. Res. 10, 1002–1018. https://doi.org/10.1007/s13346-020-00776-7

**14.** Reddy Dumpa, Nagi, Bandari, S. and Michael A. Repka. 2020. "Novel Gastro retentive Floating Pulsatile Drug Delivery System Produced via Hot-Melt Extrusion and Fused Deposition Modeling 3D Printing" Pharmaceutics 12, no. 1: 52. https://doi.org/10.3390/pharmaceutics12010052

**15.** Akram, M.R., et al. (2018). Formulation, design and development of matrix diffusion controlled transdermal drug delivery of Glimepiride. Drug Des. Devel. Ther.,12 (1): 349 – 364.

**16.** Kumar, CH., et al. (2017). Formulation and characterization of Itraconazole ethosomal gel for topical application. J. bio.Ino, 6(1): 55 – 64.

**17.** Adhyapak, AA. and Desai, B.G. (2016). Formulation and evaluation of liposomal transdermal patch for targeted drug delivery of Tamoxifen citrate for breast cancer. Indian J Health Sci., 9(1): 40 - 48.

**18.** Mateti, A., et al. (2016). Formulation and evaluation of proniosome based transdermal gel of Sumatriptan succinate. Int. J. Pharm. Biol. Sci., 6(1): 224 – 235.

**19.** Chauhan, M. and Gulati, A. (2016).Aggrandized transdermal delivery of Glimepiride via transferosomes: formulation, evaluation and stastical optimisation. J.DrugDeliv.Ther., 6(4):48 – 54.

**20.** Pandey, P. and Pancholi S.S., (2016). Nanocarrier based transdermal formulation of NSAID: optimization of drug loading and analysis of permeation characteristics. J.Innov. Pharm. Biol. Sci., 3(3): 1 – 12.

**21.** Paul,D. and Babu,VS. (2016). Formulation and evaluation of liposomal gel containing antifungal activity- Ketoconazole. Indo Am. J. Pharm. Res., 6(7): 6154 – 6169.

**22.** Sudhakar, C.K., et al. (2016). A comparison study of liposomes, transferosomes and ethosomes bearing Lamivudine. Int.J. Pharm. Sci. Res., 7(10): 4214 – 4221.

**23.** Shaik, MD., et al. (2015). Preparation and evaluation of Aceclofenac sodium proniosome transdermal patches. Int. J. Recent Sci. Res.,6(11): 7418- 7423.

**24.** Sarwa, K.K., et al. (2015). Potential of capsaicin loaded transferosomes in arthritic rats. Drug Delivery. 22(5): 638-646.

**25.** Jamshaid T. Pharmaceutics & novel drug delivery systems. Pharmaceutical regulatory affairs, 2015; 4(3):74.

**26.** Mourad AM, de Carvalho Pincinato E, Mazzola PG, Sabha M, Moriel P. Influence of soy lecithin administration on hypercholestero lemia. Cholesterol. 2010;2010:1-4. doi:10.1155/2010/824813

**27.** Küllenberg D, Taylor LA, Schneider M, Massing U. Health effects of dietary phospholipids. *Lipids Health Dis.* 2012;11:3. doi:10.1186/1476-511X-11-3

**28.** Lecithin. In: *Drugs and Lactation Database (LactMed) [Internet]*. Bethesda, MD: National Library ofMedicine; 2021.

**29.** Office of Dietary Supplements. Choline.Mourad AM, de Carvalho Pincinato E,Mazzola PG, Sabha M, Moriel P. Influence of soy lecithin administration on hypercholesterolemia. *Cholesterol*. 2010;2010:1-4.doi:10.1155/2010 /824813

**30.** Jäger R, Purpura M, Kingsley M. Phospholipids and sports performance. *Journal of the International Society of Sports Nutrition*.2007;4(1):5. doi:10.1186 /1550-2783-4-5

**31.** Bjelland I, Tell GS, Vollset SE, Konstantinova S, Ueland PM. Choline in anxiety and depression: the hordaland health study. *The American Journal of Clinical Nutrition*. 2009;90(4):1056-1060. doi:10.3945 /ajcn.2009.27493

**32.** Moré MI, Freitas U, Rutenberg D. Positive effects of soy lecithin-derived phosphatidylserine plus phosphatidic acid on memory, cognition, daily functioning, and mood in elderly patients with alzheimer's disease and dementia. *Adv Ther*. 2014;31(12):1247-1262. doi:10.1007/s12325-014-0165-1

**33.** Wang Z, Klipfell E, Bennett BJ, et al. Gut flora metabolism of phosphatidylcholine promotes cardiovascular disease. *Nature.* 2011 ;472(7341):57.doi:10.1038/nature0992 2

**34.** Stremmel W, Hanemann A, Ehehalt R, Karner M, Braun A. Phosphatidylcholine (lecithin) and the mucus layer: evidence of therapeutic efficacy in ulcerative colitis? *Dig Dis.* 2010;28(3):490-6. doi:10.1159/000320407

**35.** Latifi S, Tamayol A, Habibey R, et

al. Natural lecithin promotes neural network complexity and activity. *Sci Rep*.2016;6(1):25777.doi:10.1038/srep 25777

**36.** Velazquez R, Ferreira E, Knowles S, et al. Lifelong choline supplementation ameliorates Alzheimer's disease pathology and associated cognitive deficits by attenuating microglia activation. *AgingCell*.2019;18(6):e130 37.doi:10.1111/acel.13037

**37.** Blusztajn JK, Slack BE, Mellott TJ. Neuroprotective actions of dietary choline. *Nutrients.* 2017;9(8):815.doi:1 0.3390/nu9080815UniversityofRochest er. Lecithin

**38.** University of Nebraska Food Allergy Research and Resource Program. Soybeans and soy lecithin.

**39.** U.S. Environmental Protection Agency. Hexane.

**40.** University of Rochester Medical Center. Lecithin.

**41.** Ramdath DD, Padhi EMT, Sarfaraz S, Renwick S, Duncan AM. Beyond the cholesterol-lowering effect of soy protein: a review of the effects of dietary soy and its constituents on risk factors for cardiovascular disease. *Nutrients*. 2017; 9(4):324. doi:10.3390/nu9040324

**42.** N.K. Jain, Pharmaceutical product development, 1ed: 2006; Reprint: CBS publishers & distributers, 2008; 585–618.

**43.** V R Gowarther, RV Viewanathan, Jayadev Sreedhar, Polymer Science, 1 ed: 1986, reprint: New Age International (P) Ltd., Publishers, 2012; 12-14.

**44.** V.K. Ahluwalia, Anuradha Mishra, A Textbook of Polymer Science, 1ed. 2008; reprint, Published by Ane Book Pvt. Ltd, 2009; 19-27.

**45.** S.P. Vyas, Roop K. Khar, Controlled Drug Delivery - Concepts and Advances, 1ed: Vallabah Prakashan, 2002; 1-50, 294–229, 411-446.

**46.** N.K. Jain, Controlled and Novel Drug Delivery, 1 ed: 1997; Reprint: CBS Publishers & Distributers, 2008; 82-96.

**47.** Roop K Khar, SP Vyas, Farthan J Ahmad, Gaurav K Jain, Lachman/Lieberman's, TheTheory and Practice of Industrial Pharmacy, 4 ed, 403-448, 576-596.

**48.** Shradha Tomar, Lalit Singh, Vijay Sharma, Miraculous Adjuvants: The Pharmaceutical Polymers, Int. Res. J. Pharm, 2016; 7(7).

**49.** Naveen Kumar, Sonia Pahuja, Ranjit Sharma, Pharmaceutical Polymers - A Review, International Journal of Drug Delivery Technology, 2019; 9(1): 27-33.

**50.** Krushnakumar J. Gandhi*, Subhash V Deshmane, Kailash R Biyani, polymers in pharmaceutical drug delivery system: a review, Int. J. Pharm. Sci. Rev. Res., 2012; 14(2):10, 57-66.