International Journal of
Science, Architecture, Technology and Environment

Liposomes: A Comprehensive Review of Liposome Formulation Strategies, Mechanisms, and Therapeutic Applications

Ziarul Hoque[1], Dr. Chandra Sekhar Naik[2*]

[1]*Department Of Pharmaceutics Nimra College of Pharmacy Vijayawada 521456 AP INDIA*

[2]*Enterpreneurship Cell Coordinator Department of Pharmaceutics Nimra College of Pharmacy Vijayawada 521456 AP INDIA*

[*]*Corresponding author, chandu.desavath@gmail.com*

DOI: https://doi.org/10.63680/ijsate102673.09

Abstract

Liposomes are drug carriers system whereby the carrier is composed of one or more than one phospholipid layer(s) that surround the aqueous core. Being amphiphilic, it provides the opportunity of incorporating aqueous substances in the core and liposoluble drugs in the phospholipid layer(s). This has enabled the liposomes to play a very important part in drug formulation due to its ability to alter drug release and flexibility. This report analyses the structure of the liposomes, formation process, classification, liposome formation methods, formulation factors, advantages and disadvantages, modes of administration and applications of the liposomes. Emphasis will especially be put in long circulating liposomes, targeted liposomes, stimuli-sensitive liposomes and use of liposomes in delivering anti-cancer and antimicrobial drugs systems. Examples of commercialized liposomes will provide practical application of the technique. Despite of the numerous advantages of using liposomes drug delivery systems, there are challenges like instability of the liposomes, drug leakage, production and sterilization. Therefore, the liposomes formulations will require proper selection of lipids, vesicles, surfactants, loading and storage characteristics to overcome the challenges.

Keywords: Liposomes; phospholipids; drug delivery; targeted delivery; nanocarriers; liposomal formulations; antimicrobial therapy; cancer therapy

1. Introduction

Drug delivery systems not only offer a way of transporting an active pharmaceutical ingredient but also influence the drug distribution within an organism with regard to location, time, and conditions. There are a number of restrictions associated with traditional dosage forms such as poor water solubility, fast degradation of the drug, a short circulation time, non-specificity of the drug distribution and toxicity of the drug. Liposome delivery systems were considered as a carrier system that could help solve some of these problems. A liposome is generally spherical and is a vesicle whose components – amphiphilic lipids – self-assemble into one or more bilayers, creating an aqueous inner cavity

The molecule of phospholipid contains a hydrophilic head and a hydrophobic tail. In water medium, the hydrophilic heads tend to associate with the water molecules, while the tails attempt to stay away from water molecules. Therefore, the bilayer is created and a vesicle is formed. Hydrophilic drugs are incorporated into the inner aqueous compartment, whereas lipophilic drugs are incorporated into the bilayer. Amphiphilic drugs interact with both compartments depending on their composition and conditions of preparation.

Liposomes may protect some molecules from premature interaction with the enzyme or any other substance in biological fluids; change their biodistribution; and provide controlled/sustained release. Surface modification of the liposome may also change the circulation time or allow interactions with selected cells. However, all these features are formulation-specific – encapsulation does not automatically ensure targeting, increase in efficacy or decrease in toxicity. The final outcome depends on the drug, the composition of the lipids, the vesicles, the mode of administration, and the biological environment.

The applications of liposomes include preparations for use in pharmaceuticals, experimental protein and nucleic acid delivery, vaccine studies, cosmetics, and diagnostics. Clinical relevance of liposomes is clear from the presence of drugs being used clinically that have liposomal formulations of anticancer and

antifungal agents, among others. The current challenge is to achieve a compromise between the required delivery properties and the stability, ease of production, safety and economics of liposomes [3-8].

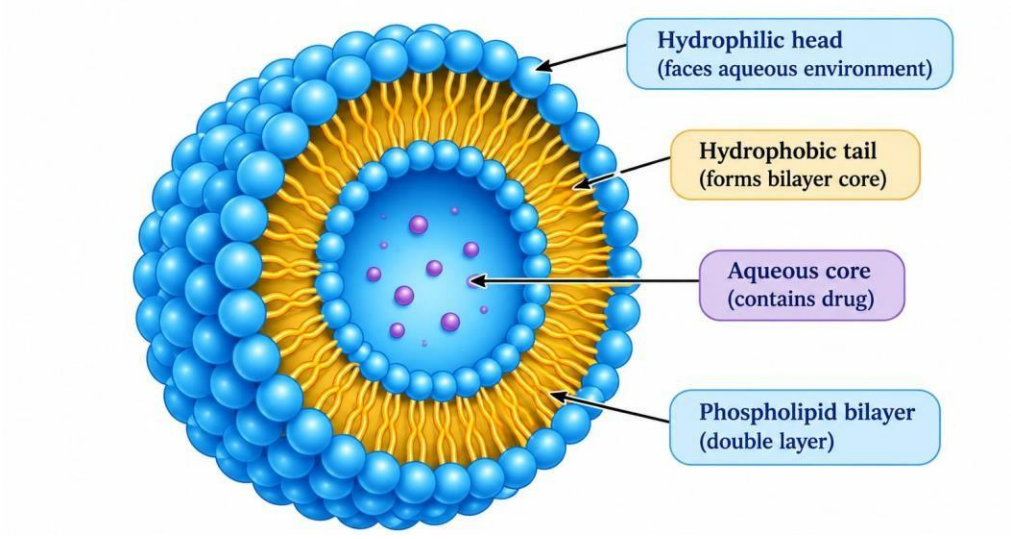


Figure 1: simple structure of Liposome

2. Historical development

The modern researches concerning liposomes were based on researches of phospholipid membranes. The researchers conducted by Alec D. Bangham and his colleagues at the beginning of 1960s showed that phospholipids in water medium can form closed two-layered structures. During this period the term "liposome" appeared and the vesicles were researched as biological membrane models and carriers of biologically active substances .

During the 1970s there was an increase in number of studies concerning delivery of drugs, enzymes, and other biological molecules using liposomes. The investigations carried out during the 1980s allowed creating more efficient technologies of liposome formation and controlling the size and composition of vesicles.

Surface modification, including those with PEG, was used to protect vesicles from fast clearance from mononuclear phagocyte system. Ligand-containing formulations were studied for better binding to chosen cells.

Liposomal drug approval was a breakthrough step towards the transfer of ideas about liposomes from scientific experiments into practice of the pharmaceutical industry. One of such drugs is Doxil – a pegylated liposomal doxorubicin, which is already FDA-approved. Other examples are liposomal amphotericin B, irinotecan, liposomal cytarabine, daunorubicin, and so on. The mentioned examples show that liposomes are not a homogeneous delivery vehicle, but rather a heterogeneous group of systems designed for certain applications.

The current field of research includes stimuli-responsive carriers, improvement of the loading efficiency, co-delivery of several compounds, and the use of lipids for delivery of nucleic acids.

Therefore, the history of liposomes is the development from the discovery of liposome structure to the design of delivery systems and drugs based on them. In any case, it should be emphasized that the development history is the description of milestones only; drug approval and its availability may differ from country to country and change with time.

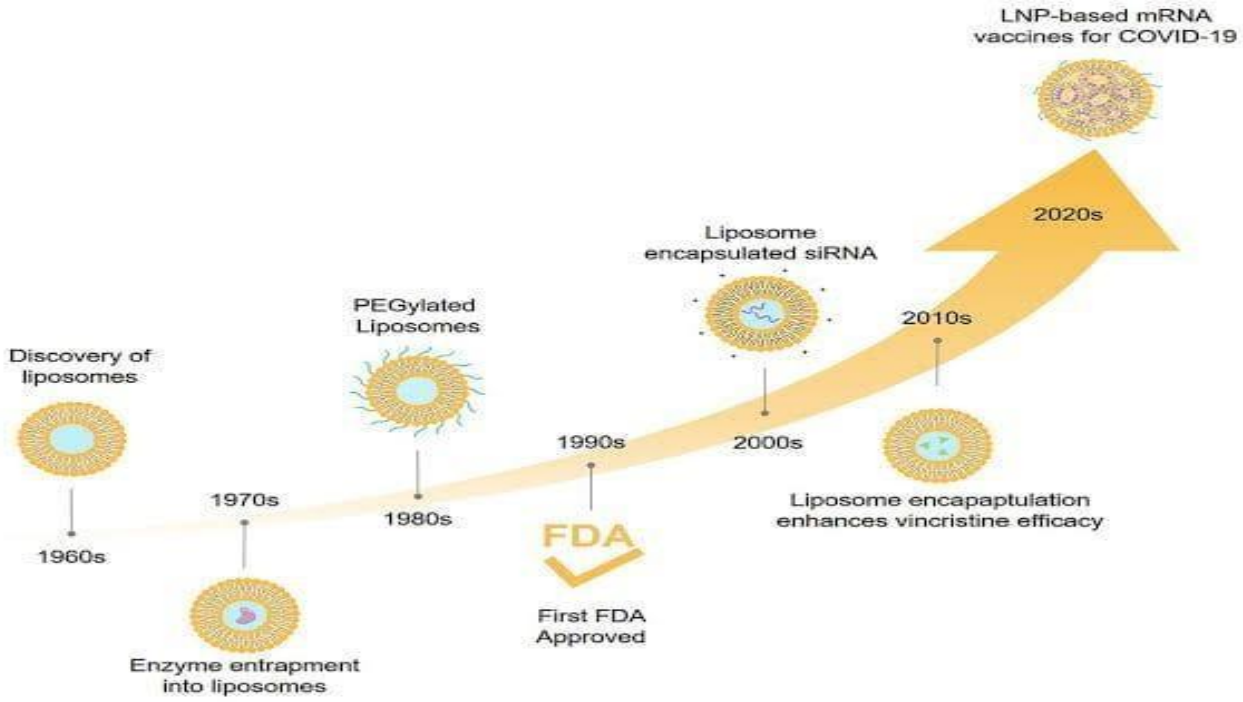


Figure 2: history and development of liposome

3. Structure and mechanism of formation

Generally, liposomes have the structure of the bilayer membrane that contains an aqueous core in the middle. Hydrophilic heads of the phospholipids are positioned facing the aqueous environment on both sides of the bilayer, whereas the hydrophobic tails face each other. Bilayer membrane is only a few nanometres in thickness, while the whole vesicle can vary from tens of nanometres to several microns depending on the preparation technique. Cholesterol could be included in order to modify such properties as lipid packing, bilayer stiffness, permeability and stability.

The main reason for formation of liposomes is the ability of amphipathic lipids to prevent unfavourable contacts between the hydrophobic tails and aqueous solution. First of all, lipids are mixed with an aqueous environment. The heads of the molecules are attracted to water, whereas the tails are repelled. Lipids spontaneously form bilayer disks. As the disks have unfavourable energy because of its edges, the membranes spontaneously form vesicles enclosing the aqueous core.

Drug entrapment depends on the physical and chemical nature of the drug and mode of preparation. If the drug is water soluble, it may get entrapped in the process of vesicle formation whereas lipophilic drugs ca get incorporated into the phospholipid bilayer. Parameters influencing drug entrapment, retention and release include lipid composition, pH, ionic strength, temperature, drug-to-lipid ratio and the permeability of the membrane.

Characterization of the formulation should be performed after its preparation. Some of the important characteristics of the formulation include particle size, lamellarity, entrapment efficiency, drug content residual solvent, if any, degradation of lipids, physical stability and drug release profile. In case of injectable formulations, sterility and endotoxins should also be considered.

4. Classification of liposomes

The liposomes can be classified either by size and number of bilayers, the kind of lipids, the surface properties, or the mode of preparation. All the above-mentioned ways of classification apply to one and the same liposome, although none excludes the others.

4.1: Classification depending on the size and lamellarity.

Multilamellar vesicles (MLVs) contain multiple bilayer membranes, which are separated from each other with aqueous spaces. MLVs are usually produced through the process of hydration of lipid film, and thus they may contain quite considerable quantities of lipophilic substances in several membranes. However, the aqueous volume within MLVs for hydrophilic substances is relatively small regarding the amount of lipids used. Large unilamellar vesicles (LUVs) contain one bilayer membrane and a considerable aqueous volume.

This makes it possible to include considerable amounts of water-soluble compounds into LUVs. Small unilamellar vesicles (SUVs) contain one bilayer membrane and have smaller diameter and volume of internal aqueous solution in comparison with LUVs. SUVs are usually produced using size reduction methods, such as sonication or high-pressure treatment.

4.2: Classification depending on composition and function.

Standard liposomes contain mainly phospholipids, cholesterol often being added to control certain properties of membranes. The surfaces of liposomes are identified by plasma proteins and become targets

for uptake by phagocytotic cells. Long-circulating liposomes ("stealth") are specially designed in order to minimize the interaction with some blood proteins and prolong the circulation time.

Acid pH sensitive liposomes have been designed for either modification of membrane properties or release properties in an acidic environment. They may prove to be useful for investigations of intracellular delivery into endosomes or diseased tissues, but an acidic medium is not the only condition needed for selective release in a certain area. Cationic liposomes are made up of positively charged lipids that bind with negatively charged nucleic acids to form complexes used in gene delivery research. The positive charge causes non-specific binding and influences the tolerance of the formulation. The ligand-targeted or immunoliposomes are liposomes that have attached antibodies, antibody fragments, peptides, aptamers or other ligands for specific recognition of cell membrane components.

4.3: Classification of liposomes according to their preparation methods.

Names such as reverse-phase evaporation vesicles or French-Press vesicles relate to formulations manufactured with certain methods. The outcome of the process depends on the entire process rather than the method used. In fact, formulations may be classified based on all four criteria – size, surface modification, lipid composition and method of production.

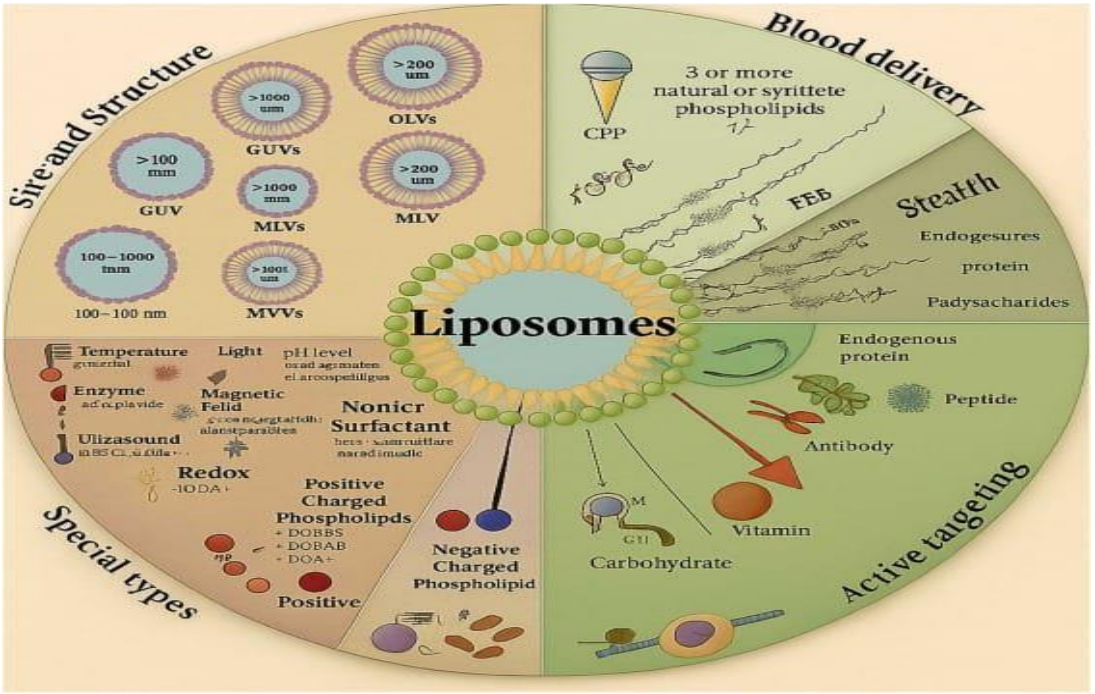


Figure 3: classification of liposome

5. Methods of preparation

Methods of preparation affect size, lamellarity, encapsulation efficiency, impurities remaining after the process, and reproducibility of liposomes. Methods of preparation should be selected in accordance with the properties of the drug and lipids, requirements of the drug product, and the scale of production.

5.1: Thin-film hydration.

The lipids are dissolved in an appropriate organic solvent. Evaporation of the solvent gives a thin lipid film. The film is hydrated by an aqueous solution resulting in a dispersion containing multilamellar vesicles.

Additional operations such as extrusion or sonication may provide reduction and narrowization of size distribution. It is a commonly used method for preparation of liposomes, but in some cases additional operations may be required to produce liposomes of a certain size and high encapsulation efficiency.

5.2: Sonication.

The suspension of liposomes is subjected to ultrasonication in a bath or probe sonicator. As a result of cavitation and shear forces large vesicles are converted into small vesicles, and even SUVs. This is a useful laboratory method of liposome size reduction. However, the following factors have to be taken into consideration: temperature increase, lipid degradation, leakage, contamination by the probe, narrowization of size distribution.

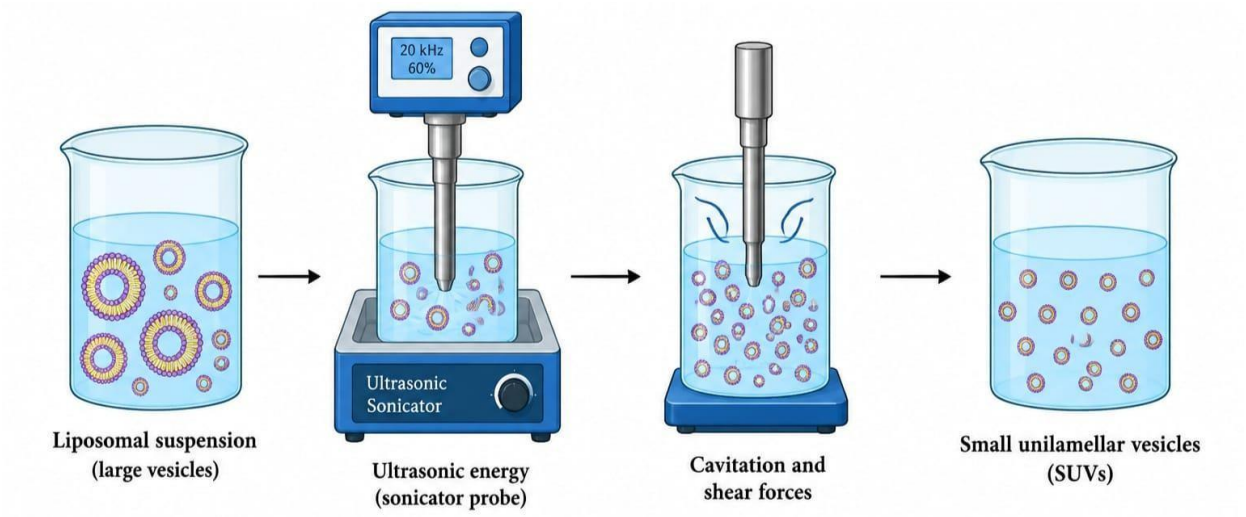


Figure 4: sonication method

5.3: Extrusion or Filtration using Membranes.

Prepared liposome suspension is made to pass through membranes with pore sizes specified in advance.

Continuous passing leads to a decrease in particle size and uniformity increase. Particle size after the treatment depends on pore size, number of passes, pressure, vesicle properties, and suitability of the membrane to the process. Membrane clogging, product losses, and necessity of pressure control can be challenges in this case.

5.4: French Pressure Cell and High-Pressure Processing

Pressure techniques imply the passage of vesicle suspensions through limited space at a high pressure or shearing force. The above methods can provide smaller and more uniform vesicles, yet special equipment is needed for such procedures. Temperature rise and leakage of drugs into the environment can occur in these cases and process suitability should be studied prior to scaling up.

5.5: Freeze-thaw processing.

Vesicle suspension is being frozen and thawed. Sonication or extrusion can follow it. Freezing and thawing influence vesicle structure and solute distribution within the vesicles.

5.6: Solvent-injection methods.

If using ether or ethanol injection method, lipids that are dissolved in the organic solvent are injected into the aqueous phase. Lipid organization and vesicle formation occur either upon mixing or evaporation of the solvent in the aqueous system. Ether injection requires heating and evaporation of the solvent. Residual solvents need to be controlled. Ethanol injection is rather convenient, but residual ethanol and rapid mixing need to be controlled.

5.7: Reverse-phase evaporation.

In this case, lipids are dissolved in the organic solvent and are combined with the aqueous phase forming water-in-oil emulsion. Removal of the organic solvent leads to formation of bilayer vesicles. The method allows obtaining relatively high aqueous entrapment for suitable substances, but requires use of organic solvents, effective solvent removal, and sensitive drugs may be damaged due to mixing or processing.

5.8: Detergent-removal methods.

First of all, lipids and detergent are mixed resulting in the formation of mixed structures. Further, the detergent is removed using dialysis, dilution, or separation procedure.

Bilayer vesicles can form. The detergent needs to be removed down to the necessary level. The method includes control of the composition and processing conditions.

6. Advantages, limitations, and formulation factors

The main advantages of liposomes include their capability to deliver lipophilic and hydrophilic compounds, to stabilize some drugs and to affect distribution and release. The lipid composition could be suitable for biology, and surface modification could help in increasing circulation time and targeting ligands. In some cases, encapsulation could reduce the contact of some healthy tissues with the unencapsulated compound. These are some possible benefits, not obligatory features of all liposome systems.

Some disadvantages of liposomes include their physical instability, aggregation, fusion, release of incorporated cargo, and chemical degradation due to lipid oxidation and hydrolysis. Some formulations are difficult to sterilize without affecting liposomes and loaded drug. The technology is likely to be costly, and scaling could lead to changes in the particle size distribution, drug loading and release rate. Liposomes are rapidly cleared by macrophages. PEGylation prolongs circulation, but doesn't prevent biological interactions.

Several factors that influence performance need to be considered. Lipid structure and composition influence membrane packing, phase behavior, permeability, and compatibility. Cholesterol reduces membrane permeability and leakage of some systems; nevertheless, the influence of cholesterol depends on the kind of lipid mixture used and temperature. Vesicle size and membrane lamellarity influence aqueous volume content, loading capacity, circulation, cellular uptake, and release. Surface charge influences aggregation and interaction with proteins and cell membranes. Molecular weight, solubility, ionization state, lipophilicity, and charge of the drug influence the drug site and retention.

The formulation can be affected by several factors including the concentration of the lipids, hydration conditions, pH, ionic strength, temperature, mixing time, solvent removal techniques, sonication energy, pressure, and number of extrusion cycles. Factors such as temperature, light, oxygen exposure, compatibility with containers, and storage time influence the stability of the formulation. It is therefore necessary to have a systematic approach to formulation whereby the target product profile is determined, lipids and drug loading techniques are selected, process parameters optimized, critical quality attributes determined, and stability studies under justified conditions.

7. Role in pharmaceutical practice and routes of administration

It is one of the methods utilized in the pharmaceutical industry for the modification of the drug solubility, stability, biodistribution, and release. This is because the delivery method may affect an important property of the active substance. The delivery of certain anticancer drugs using the liposome method may modify the biodistribution of drugs while the delivery of antifungal and antimicrobial drugs is another example.

Delivery of proteins, peptides, antigens, and nucleic acids is another utilization of the technique. Liposomes are not supposed to be taken as an enhancement of the absorption and efficacy of the medicine by all means of administration.

Intravenous administration liposomes have direct access to the bloodstream. The liposome method is employed in the delivery of some already approved liposomal drugs. The delivery method will influence the circulation and distribution and therefore must be produced under very strict standards concerning sterility, particulate matter, and other quality factors. Liposomes delivered orally have been tested to provide protection against the breakdown of active ingredients in the gastrointestinal tract.

Routes which provide topical and transdermal effects are explored with a view of using them for local skin delivery or skin barrier crossing. This is quite different. Topical administration aims for the effect at the site of administration, while transdermal administration is concerned with the crossing of skin barrier.

Pulmonary administration can also deliver the drug to the lungs if the aerosol has good performance, stability and lung tolerance. The nasal route might also be considered for local or systemic delivery.

Liposomal preparations for the ocular administration are also developed to prolong their contact time or local delivery. Intramuscular and subcutaneous administration can also be employed for certain preparations, including depot type applications. Different routes result in different barriers, safety concerns and quality control criteria. It is wrong to use a liposome for one purpose by assuming that it works for another purpose.

8. Recent approaches and therapeutic applications

Lately there have been approaches proposed in order to improve the targeting ability, increase the circulation time, control release, and allow the delivery of hard-to-deliver molecules. The ligand-targeted liposomes are the ones which consist of some surface molecules which are designed to bind to the receptors or antigens specific to the targeted cells. This binding might be helpful in order to improve the interaction of liposomes with the target cells; however, this does not guarantee the full targeting of the dose to the target tissue/cells. Biological barriers and distribution of the target molecule play an important role as well.

The stealth liposomes are the ones which have been subject to surface modifications like those which contain PEG chains on their surface. These are used to minimize the protein interactions as well as the clearance. There are some liposomes which are designed to respond to some stimuli in terms of structure or release. For instance, there are some pH-responsive, temperature-responsive, enzyme-responsive, redox-responsive, light-responsive, magnetic field-responsive, and ultrasound-responsive liposomes. There have been developed dual-responsive liposomes which are responsive to more than one stimulus.

8.1: Anti-cancer treatment.

The system could alter the pharmacokinetic properties and distribution of anti-cancer agents. Examples of clinically approved medicines include liposomal doxorubicin and liposomal irinotecan. Despite that liposomal delivery alters toxicity and exposure properties, indication and side effect profile vary depending on the particular preparation. It is very important to understand the difference between the liposomal medicine and the non-liposomal form since their dosing equivalence could be different.

8.2: Antimicrobial and antifungal treatment.

Liposomes might be used as a shield to protect the antimicrobial agent, influence distribution and intracellular uptake of the drug. One example is liposomal amphotericin B which is used as a clinically available drug to treat serious fungal infections. Studies also focus on delivery of the drug to the intracellular pathogens or those in which there is no sufficient exposure to the free drug.

8.3: Gene and Nucleic Acid Delivery.

Cationic or ionizable lipids are capable of forming complexes of nucleic acids and delivering them inside cells. Formulation takes care of the protection of nucleic acid, cellular uptake, and intracellular release, as well as the avoidance of any potential toxic effects or immunological response. Properties of these formulations include charge, lipid content, liposome size, and liposome composition.

8.4 : Vaccines and Biological Agents.

Liposomes can carry antigens and adjuvants and thus influence immune system interactions. Liposomes have been suggested as a carrier system for proteins and peptides that might be susceptible to degradation by enzymes. Stability and immunogenicity of these biological cargos depend on the particular formulation used.

8.5: Cosmetics, Diagnostics and Research.

Liposomes are utilized as a carrier system for certain cosmetics as well as for diagnostics, radiopharmaceuticals, imaging, and as models of biological membranes. Such uses have different criteria than pharmaceutical formulations.

9. Marketed liposomal products

Examples of marketed products give concrete examples as to how liposomal delivery systems are designed based on the type of drug or compound that is being delivered and its application. Examples that have been given in the review article include the following: Approvals, applications, modes of delivery, and marketing status can differ from one country to another; the information below is for reference only.

Product	Active ingredient	Broad use described in the supplied review	Route described
Doxil	Doxorubicin hydrochloride	Selected cancers	Intravenous
AmBisome	Amphotericin B	Serious fungal infections	Intravenous
Marqibo	Vincristine sulfate	Selected cases of acute lymphoblastic leukaemia	Intravenous
Onivyde	Irinotecan hydrochloride	Metastatic pancreatic cancer in a specified regimen	Intravenous
Vyxeos	Daunorubicin and cytarabine	Acute myeloid leukaemia in specified settings	Intravenous
Arikayce	Amikacin sulfate	Lung disease due to Mycobacterium avium complex	Oral inhalation

These examples must be confirmed via current regulatory product information before the thesis writing, particularly in case indications are specified and/or mention about availability of certain products in certain jurisdictions is included. Liposome-based preparations differ from the conventional analogues in dosage, route of administration, pharmacokinetics, contraindications, and side effects. The usage of liposomes in medicine will depend on the labelling and protocol used for treatment.

The existence of liposome-based products on the market is a proof of technological possibility of production of liposomes and their usage in medicine, although it does not mean that all liposome-based products will be successful. There are several problems that have to be solved during the development of the products, including validation of the process of production, adequate analysis methods, stable batches, and safety.

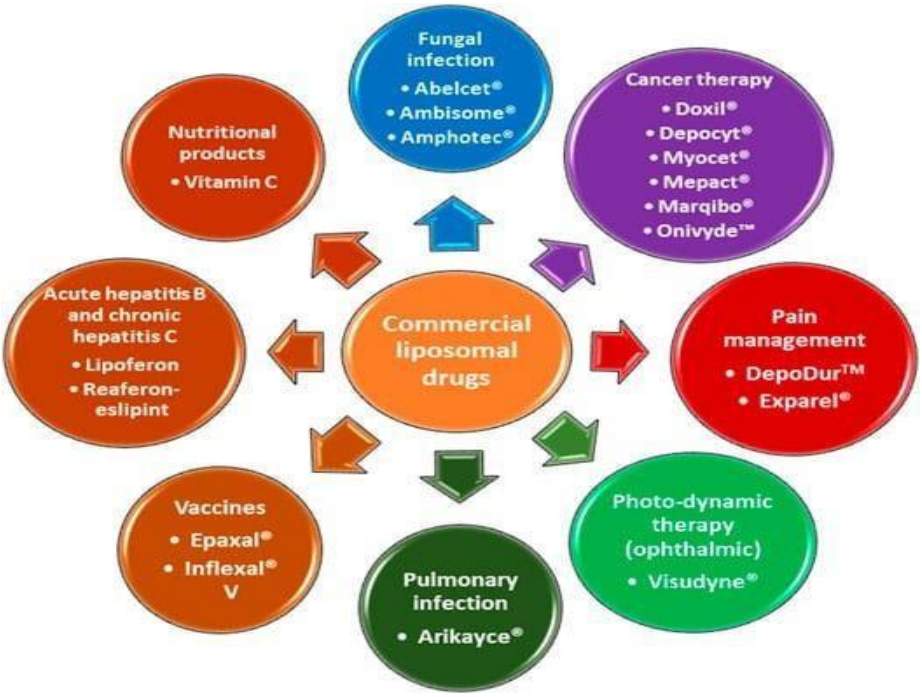


Figure 5: marketed drugs

10.Challenges, quality considerations, and future prospects

The success of liposomes in drug delivery depends on the solving of problems associated with their formulation and manufacture besides biological challenges. First and foremost, it is necessary to achieve an optimal drug loading, to preserve the drug during the storage and circulation period, followed by the controlled release of the drug at the target site. A formulation which is able to accommodate a large quantity of drug but leaks rapidly does not perform its purpose, although a formulation preserving the drug may be inefficient for the delivery of a sufficient dose of the active substance.

Physical characterization of the formulation may include the analysis of the particle size and size distribution, morphology, lamellarity, aggregation state. Chemical characterization may consist of the drug content, lipid composition, degradation products, residual solvents. Functional evaluation may include the assessment of the encapsulation efficiency, leakage rate, release profile, biological efficacy. The stability testing programmed should consider the proposed storage conditions, transport, container/closure system and handling procedure. Sterile products require special microbiological controls and validation.

Scale up is not just about making a bigger batch since mixing, heat transfer, solvent loss, filtration and residence times will change based on the machinery and batch size used. Thus, it is important that process variables be linked to critical quality attributes using manufacturing control methods. Measurement methods for robust determination of particle size, free /encapsulated drug release must be developed to ensure consistency from batch to batch and to compare formulations.

For the future there is potential for greater targeting specificity, responsiveness of release, co-delivery, and nucleic acid/biological macromolecule transport. Better models and characterization of formulations would be useful to understand how formulations affect biological action. More complicated formulations might make manufacturing difficult and costly, though. The greatest innovation isn't necessarily the most complicated formulation but the one with proven superiority over current technology.

It is important to mention a balanced analysis, when the distinction between those drugs which are proved by clinical trials and the research programs is obvious. The data received during laboratory researches need further confirmation through certain studies, including the claims about increased efficacy or safety of this preparation. There are numerous possibilities for liposomes, but in any case, it should be proved.

11. Liposome Characterization and Evaluation

I. Summary:

It is extremely important to characterize liposomes properly because the properties of liposomes depend on many parameters including size, size distribution, surface properties, lamellarity, composition, and drug content. Characterization cannot be performed with the help of a single method and appropriate methods

should be chosen according to the specific formulation and the administration route.

II. Particle size and distribution:

The hydrodynamic size and polydispersity index can be measured via dynamic light scattering. These measurements may be influenced by some parameters including dust presence, aggregation, the

concentration of the sample, and underlying assumptions. Electron microscopy will give information about the shape of vesicles, while the particle tracking analysis might help to measure size and concentration of particles.

III. Zeta Potential and Colloidal Stability:

Zeta potential is an electrokinetic potential close to the surface of a particle, and it can assist in determining the colloidal properties. Zeta potential cannot be employed as a universal tool for shelf-life evaluation. There are sterically stabilized systems with low zeta potential but high stability (for example, systems with PEGs). These findings must be considered in conjunction with the formulation composition, ionic strength, and pH.

IV. Entrapment Efficiency and Drug Loading:

Entrapment efficiency is the proportion of drug in relation to the initial amount of the drug encapsulated in liposomes. Drug loading is the ratio of drug content to the specified amount of lipids/formulation. The free drug must be removed from the sample using proper techniques, such as size-exclusion chromatography, dialysis, ultrafiltration, or centrifugation.

V. Morphology, lamellarity, and release:

Microscopy and specialized structural methods can assess morphology and lamellarity. In vitro release testing can compare formulations and investigate the effects of membrane composition, temperature, pH, and sink conditions. Such data support formulation comparison but do not alone establish release behavior in living systems. Test conditions should be justified and discriminating.

VI. Morphology, lamellarity, and release:

Microscopic methods and specific structural investigations may be helpful in assessing morphology and lamellarity. In vitro release experiments may be performed for the comparison of formulations and

investigation of effects of the nature of the membrane, temperature, pH, and sink studies. This information allows comparing the formulations but is not enough to reveal the release pattern in vivo.

12.Stability, Storage, and Quality Control

I. Physical and chemical instability:

Liposomes may display aggregation, fusion, leakage, size distribution changes, or alteration in lamellarity. Chemical instabilities include lipid oxidation and ester bond hydrolysis. They affect drug stability, retention, distribution, safety, and efficacy. Use of appropriate buffers, avoidance of light exposure, antioxidant addition, control of headspace, and packaging should be considered, if needed.

II. Storage and reconstitution:

The storage conditions should be determined experimentally for each drug product. For some drugs, liposome dispersions are used; in other cases, freeze-dried products are available for further reconstitution. Freeze-drying may improve stability for certain liposomal drugs. Freezing and drying processes may cause destabilization of liposomes in certain cases.

III. Attributes of quality and batch to batch consistency:

A risk-based quality control strategy may encompass lipid characterization and quantification, drug characterization and quantification, free drug content, particle size and distribution, pH, osmolality if applicable, appearance, sterility, endotoxins, and impurity profiling. The final list depends on the nature of the product and applicable requirements. Control of manufacturing should consider variability of raw materials, process-related, filling and compatibility with containers.

IV. Studies for establishing the stability indicating methodology:

Stability studies involve testing the product under particular storage conditions during certain period of time.

Rationale for the sampling scheme, analytical methodology, acceptance criteria, and packaging should be provided. In case of liposome products, both drug and carrier have to be tested, because drug content

analysis does not prove vesicle integrity.

13.Translational Considerations and Future Directions

- **Manufacturing and Scale-Up:**

There may be variations in the way these methods work when the batch size, flow rate, mixing pattern and time of residence change. Process development should be aware of the factors that greatly affect the quality attributes. The use of continuous or intensified manufacturing techniques can increase reproducibility but equipment, process and validation should be in place.

- **Physiological Barriers and Individual Variation;**

Liposomes will interact with proteins, immune cells and blood vessels when they are administered. These interactions may alter the behavior of liposomes as well as their distribution. The delivery of liposomes to tumors will depend on the vasculature, tissue structure, stage of the tumor and previous therapy.

- **New Design Strategies:**

There is literature dealing with stimuli-responsive liposomes, targeted surface modifications, multifunctional cargo, and formulations optimized for specific tissues or organs. Higher complexity adds to difficulties in manufacturing and potential problems in analysis or regulatory issues. It would be necessary to have an

apparent benefit of the design compared to a simpler formulation supported by appropriate evidence.

- **Future Research;**

Possible directions of future research might be related to standardization of analysis methods, closer links between in vitro and in vivo properties, better prediction of long-term stability, and manufacturing at large scale. Benefit/risk balance including tolerance, immunogenicity, delivery needs, and economics should be evaluated. Clinical success would depend on appropriate formulation/therapy match.

14. Conclusion

Liposomes are versatile structures which consist of phospholipids and have the capacity to transport both hydrophilic and lipophilic compounds within the different compartments of the liposomes. The composition, size, lamellarity, surface properties, and manufacturing process of the liposomes may be modified to impact on the performance of the drug contained in them.

However, there may be complications in relation to the liposomes in terms of leakage, aggregation, fusion, and breakdown of the lipids. Complications arising from sterilization, scale-up, quality control, and costs may

be some of the challenges associated with the manufacture of the liposomal drug. It is essential that there is adequate formulation and characterization of the drug to show its usefulness.

Clinical applications demonstrate the usefulness of the liposomal delivery system; on the other hand, there are continuously new approaches being developed due to target-specific and stimulus-sensitive formulations. Future innovations will depend on our capacity to implement these technologies into commercial products.

Liposomes can be viewed as a versatile drug delivery system, whose possibilities are great but must be confirmed individually for every single formulation.

AKNOWLEDGEMENTS:

The author is thankful to Guide Prof Dr. Chandra Sekhar Naik, Professor Enterpreneurship Cell Coordinator Nimra College of Pharmacy for advice in writing this Article.

Declaration of Conflicting Interests:

The authors declare no potential conflicts of interest with respect to the research, authorship and publication of this article.

Funding:

The author received no financial support for the research, authorship and publication of this article.

15.References.

1. Bhaskaran M, A Text Book of Novel Drug Delivery Systems. Jalandhar: S. Vikas and Company (PV Books); 2019.
2. Mishra K. Novel Drug Delivery Systems. New Delhi: New Age International (P) Limited, Publishers; 2019
3. Reddy KVVN, Narukulla S. A Text Book of Novel Drug Delivery Systems. Jalandhar: S. Vikas and Company (PV Books); 2019.
4. Prajapati ST. Novel Drug Delivery System. Lucknow: Thakur Publication Pvt . Ltd.; 2019.
5. Narukulla S. A Text Book of Novel Drug Delivery Systems. Jalandhar: S. Vikas and Company (PV

Books); 2019

6. Katedeshmukh RG. Novel Drug Delivery System. Lucknow: Thakur Publication Pvt. Ltd.; 2019
7. Jain AK. Novel Drug Delivery Systems. New Delhi: New Age International (P) Limited, Publishers; 2019
8. Manivannan R. Novel Drug Delivery System. Lucknow: Thakur Publication Pvt. Ltd.; 2019