Review Article

LIPOSOME NANOPARTICLES FOR THERAPEUTIC AND DIAGNOSTIC APPLICATIONS

Abstract

LNPs mix liposomes and inorganic/organic nanoparticles. Liposomes and nanoparticles are therapeutic. LNPs are a research tool (e.g., spatiotemporal control of drug release, hyperthermia, photothermal therapy, and biological imaging). Nanoparticles determine LNP characteristics. Nanoparticles enable liposomes overcome weak stability, few functions, and fast blood elimination. Structure, physicochemical properties, modification, and biological uses of nanoparticle materials and LNPs are reviewed.

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Keywords: Liposome nanoparticles; Combination Therapy; Controlled Drug Delivery system; Nanostructure

Introduction

Liposomes are formed from cholesterol and non-toxic non-phospholipids. Liposomes' small size, hydrophobic and hydrophilic characteristics promise drug delivery (as well as their biocompatibility). Lipid composition, surface charge, diameter, and manufacturing procedure can affect liposome quality. The bilayer's components determine its 'rigidity' or 'fluidity' and charge. Unsaturated phosphatidylcholine bilayers (egg or soybean) are more permeable and less stable than saturated bilayers with lengthy acyl chains (for example, dipalmitoidoylphosphatidylcholine). Phospholipids form closed structures when hydrated in water. Vesicles with phospholipid bilayer membranes can deliver aqueous or lipid medications. Their amphipathic abilities and self-assembling features influence the entropically focused seizure of their hydrophobic sections into two-dimensional bilayers in aqueous fluids. Strata are called lamellae [4]. Most liposomes are cylindrical, with sizes of 30 nm to several micrometres.

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One or more lipid bilayers may encircle water units, with polar head groups aligned with inner and outer phases. Even with typical bilayer structures, which depend on molecule shape, temperature, ambient and preparation conditions, etc., self-assembly into colloidal particles is conceivable [5].

Liposomes are used to carry chemicals in the beauty and pharmaceutical industries. In the food and farming industries, liposome encapsulation has been used to safeguard unstable chemicals (such as antimicrobials, antioxidants, flavours, and bioactive components). Liposomes can entrap hydrophobic and hydrophilic molecules, block their breakdown, and release them at specified places [6-8].

Due to their low toxicity, biocompatibility, biodegradability, and ability to trap hydrophilic and lipophilic medications, liposomes have gained favour as a drug delivery device [9, 10]. Liposomes can minimise medicine toxicity and/or target specific cells [11-13].

Researchers are using LET, or liposomal encapsulation technology, to deliver therapeutic promoters to crucial organs (LET). This approach gave vital combinations to the body. LET creates liposomes, which can encase various molecules. These 'liposomes,' which are generated in the human body, are resistant to free radicals, digestive enzymes, alkaline solutions, bile and stool salts, and intestinal flora. Liposomes' lipids protect their contents from oxidation and degradation. When liposome contents are delivered to the correct gland, organ, or system, the phospholipid barrier remains [14].

The clinical medication supply grows rapidly as new treatments are licenced each year. Every drug-based therapy aims to maximise efficacy and minimise negative effects. Most conservative chemotherapeutics have toxic side effects on normal tissues and organs, limiting their clinical usage. This challenge can be solved in many ways, but "selective" delivery of medication to sick cells, tissues, and organs is optimal. These include colloidal particles and conjugated compounds. Reverse micelles, noisomes, micro- and nano-spheres, erythrocytes, and liposomes are colloidal particles. Liposomes get the greatest attention. They're biodegradable and biocompatible. Liposomes have lipid bilayers surrounding an aqueous centre. These products are made from biologically inert, weakly immunogenic phospholipids with low toxicity. The lipid bilayer can encapsulate lipophilic pharmaceuticals, whereas the aqueous compartment can only hold

hydrophilic drugs. Drugs with an intermediate logp partition easily between the bilayer and aqueous core [15].

This review focuses on liposome production, covering preparation, characterisation, determining factors, and advantages and downsides. We review the research on long-circulating, stable liposomes (stealth liposomes) and their usefulness.

Classification of Liposomes

Liposomes are malleable substances that can be synthesised in several ways. Their structure, size, shape, and surface features vary. Size and layer count classify unilamellar and multilamellar liposomes. Based on structural properties, they can be classified as multilamellar vesicles, oligolamellar vesicles, multilamellar liposomes/vesicles (MVV), and unilamellar vesicles (ULV). ULVs are categorised by size as gigantic (GUV), big (LUV), medium (MUL), and tiny (SUV) (ULV). Fig:1 GUV includes huge unilamellar liposomes and VESICLES (SUV). Despite the classification of liposomes above, many properties, such as production techniques and applications, remain unknown. Numerous ways have been developed for producing liposomes as lipid-carrying particles. Depending on the intended usage, each has advantages and downsides. Because the manufacturing process affects liposome characteristics, it should be carefully planned. Liposomes have an extremely variable structure in terms of charge and dimensions,

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with their final size and electrical charge heavily dependent on the production technique and phospholipids utilised. Dehydration and rehydration, reverse phase evaporation, extrusion, and frozen and thawed are liposome production processes.

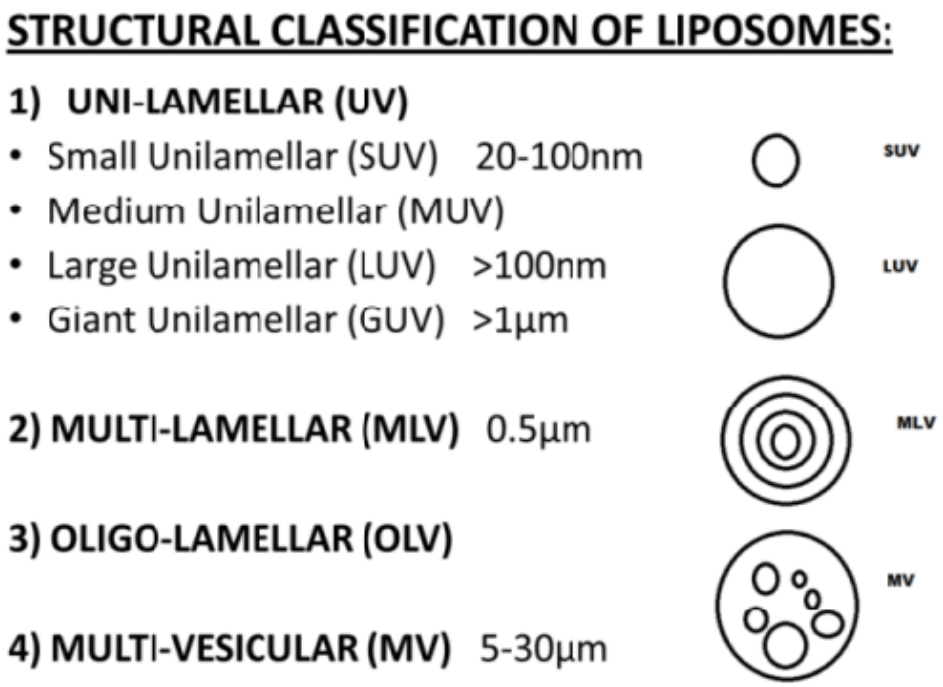

Fig: 1 Classification of Liposomes

Application of Liposomes in preparation of Medicine

Liposomes can modify drug distribution in the body, reducing side effects and improving therapeutic efficacy. Therapeutic or diagnostic applications of liposomes carrying medications or other substances; fundamental investigations of cell interfaces, recognition methods, and the mechanism of action of specific materials. (fig. 2), (

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Depending on how they interact with cells and what happens in the body after administration, liposomal drug carriers have advantages and downsides. Liposomes interact with cells in vitro and in vivo by adsorption or endocytosis. Membrane fusion is uncommon. Fourth, bilayer components like cholesterol and lipid can interact with cell membranes. These interactions affect liposomes' in vivo fate. Humans have a complex defence system. Smaller particles, germs, bacteria, and colloids are eliminated by the immune system as soon as they enter the body, triggering thrombus formation and then bio macromolecule passivation. Due to the immune system's response, attempts have been made to build biocompatible and non-recognizable surfaces and to limit micro particle drug carriers to immune system cells. Despite being formed of natural substances, liposomes aren't rare. Spleen, liver, and bone marrow macrophages remove them swiftly.

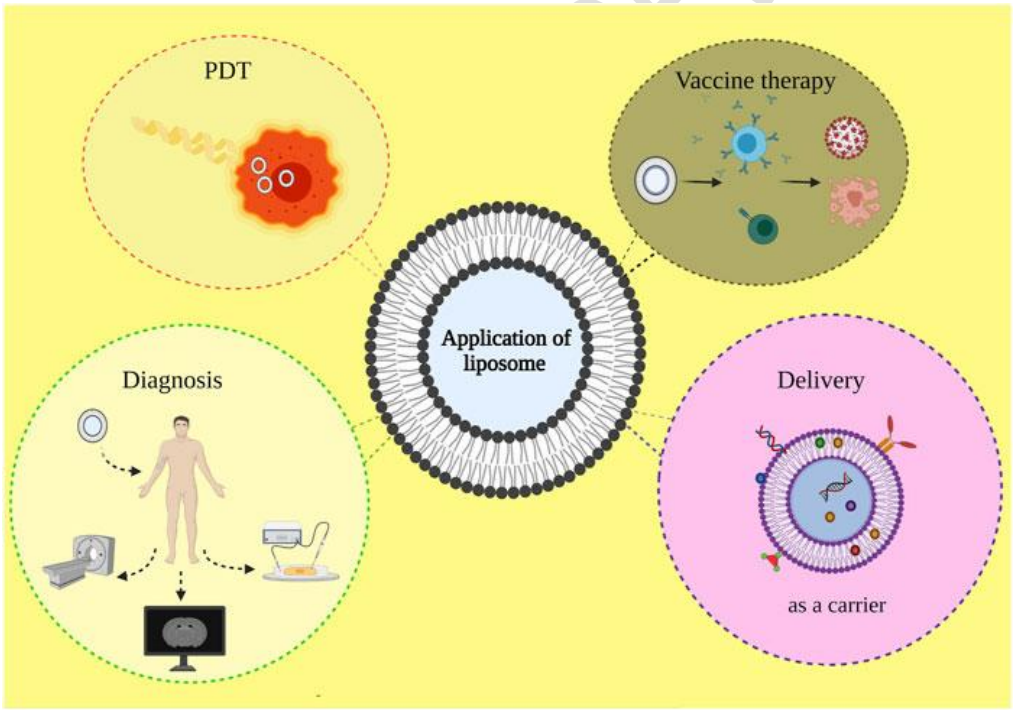

Fig: 2 Liposomes biological Application

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Liposomes have been widely explored in drug delivery to malignant and tumour tissues via passive and active targeting (Figure 3). Passive targeting depends on tumour and nanoparticle properties. Due to their high metabolism, cancer cells overexpress VEGF, leading to excessive angiogenesis. Tumor tissue has larger vascular pores than normal tissue, hence the anti-cancer medication nanosystem might target tumour tissue. Due to lymphatic system abnormalities, nanoparticles retain drugs longer in malignant tissue than tiny drug molecules. In this approach, the nanosystem is coated with a biocompatible PEG polymer, which escapes the reticuloendothelial (RES) system and enhances circulation time; PEG shields liposomes from opsonization.

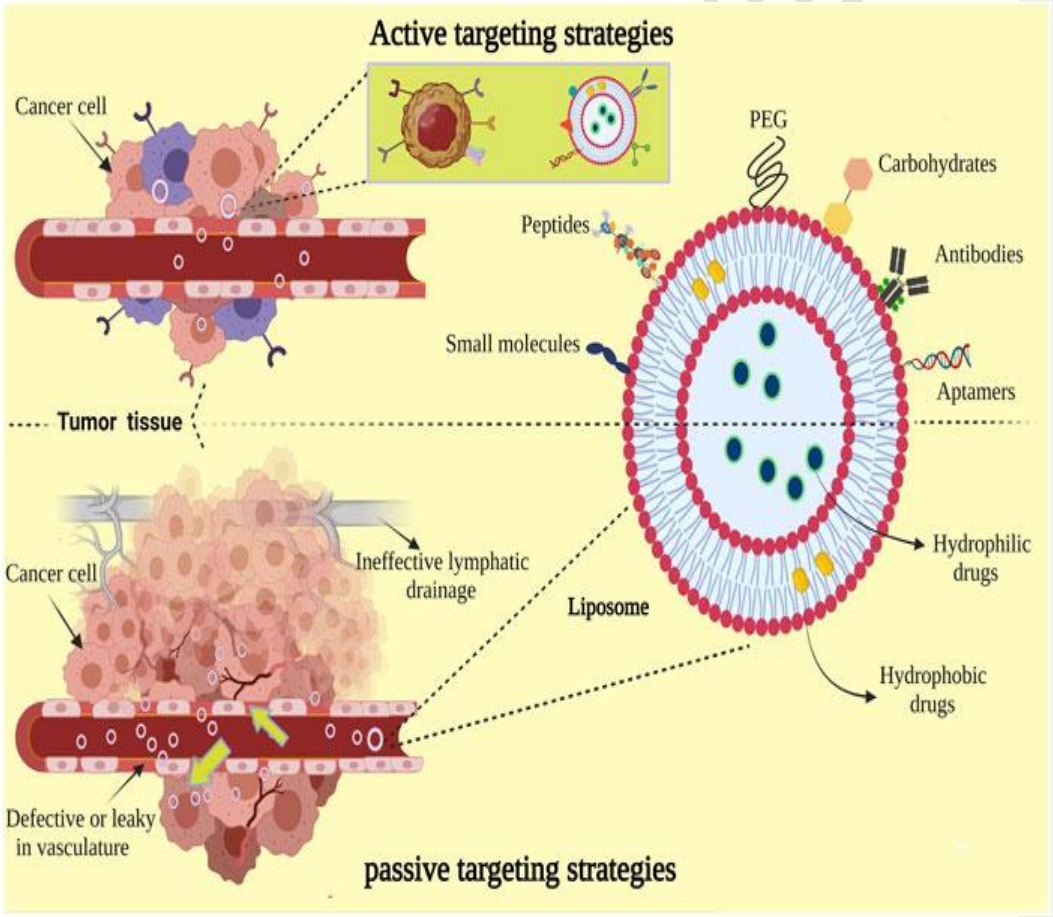

Fig: 3 Targeting passively and actively. Liposomes can be PEGylated for stealth and targeted with antibodies, peptides, proteins, carbohydrates, Aptamer, and other small molecules to improve receptor-mediated endocytosis. PEGylation increases in vivo liposomal half-life. Drugs can be enclosed in the aqueous lumen, integrated into the lipid bilayer, or conjugated to the liposome surface.

Methods for Preparation Liposomes

Thin flim Method

Liposomes can be made in a laboratory by hydrating a thin film and extruding it. When a lipid film needs to be formed, the organic solvent in a round-bottom flask is drained off and replaced with water. Liposomes are formed when dispersion fluid is agitated. Liposomes of homogeneous size are produced by extruding polycarbonate membranes. Liposomes are made using thin-film methods. In this process, fat is heated and evaporated by rotating flasks that coat the inner wall. The film is moistened with either water or a buffer solution before it is exposed to light. Hydration of lipid film and water/buffer solution can be improved by preheating the lipid film and solution. Liposomes are formed when the flask lid is peeled off and vigorous shaking and ultrasonication are applied. Different-sized MLVs are used in liposomes.

Pro-Liposomes Method

When in contact with water, proliposomes produce a liposomal suspension. They are small, free-flowing particles with a scattered system. Proliposomes outperform ordinary liposomes when it comes to increasing drug absorption. It is possible to enhance liposomes' physical stability without affecting their intrinsic properties because of their solid nature. Since hydrophobic medications have difficulty being absorbed through the mouth, proliposomes could be a useful delivery system. The presence of bile salts in the gastrointestinal tract, which can interact with phospholipids to generate mixed micelles for vehicles/mesophases to boost the solubility of

hydrophobic medicines, may be part of the underlying mechanism that allows proliposomes to improve oral absorption.

Ethanol Injection Method

Small unilamellar liposomes can be made quickly and easily using the ethanol injection approach, which has been well-documented in the literature. A number of variables have been found to affect the results of this process, and modifications have been made to the technique in order to achieve small, homogenous liposomes. An in-depth look at ethanol injection and the alterations that were made is provided in this review article. It's also important to take into account factors like injecting at a fast enough speed, stirring quickly enough to keep the aqueous phase homogeneous, and injecting via a large enough hole to accommodate large enough volumes of aqueous phase lipid.

Pharmacological Difficulties Liposomal Delivery Systems

The field of delivery methods for medicinal agents or natural-based active chemicals has recently undergone substantial advancements [33, 34] in recent years. While many drug delivery methods have been effectively deployed in recent years, there are still a number of obstacles and new technologies needed to ensure the successful delivery of the pharmaceuticals they are intended for. As a result, researchers are working to develop drug delivery methods based on nanotechnology.

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Liposome Clearance and RES

RES removes foreign particles from the body, aiding host defence. We've tested RD-influence LPS's on RES activity." Scientific methods eliminate 99mTc-labeled nanoalbumin microcolloid from blood. This approach detects granulopetic activity and efficiency. The granulopectic index of the RES clearance curve was exponential. Liver, spleen, and bone marrow cells absorbed 99mTc-labeled nanoalbumon microcolloid. RES damage was measured by colloid clearance and organ distribution. Radiation and alcoholism have been studied. Liver, spleen, and bone marrow showed decreased phagocytic activity and colloid clearance. High doses of LPS harm the RES system, but RD-LPS stimulates phagocytosis. RD-LPS can reduce or eliminate RES-damaging chemicals' negative effects. Increasing RES activity should boost natural resistance [44,45].

Nanoparticles must overcome the reticuloendothelial system (RES). Polyethylene glycol-modified nanoparticles reduce target cell internalisation. We designed a "don't-eat-us" RES-specific blocking technique. First, liposomes were coated with CD47-derived peptide ligand (d-self-peptide-labeled liposome, DSL). After mainline distribution, DSL adsorbs onto hepatic phagocyte membranes (including Kupffer cells and liver sinusoidal endothelial cells), forming a long-lasting mask that reduces phagocyte-nanoparticle interactions. DSL stopped RES at a lower dose and for longer than CL, lengthening nanoparticle half-life. This "don't-eat-us" strategy by DSL was evaluated on brain-targeted delivery against a cryptococcal meningitis model, giving dramatically enhanced brain accumulation and superior therapeutic efficacy of Amphotericin B compared with CL. Masking phagocyte surfaces prevents RES, prolongs nanoparticle circulation, and improves nanoparticle distribution.

Opsonins destabilise vesicles

All cells emit submicrometer-sized lipid-membrane particles called extracellular vesicles. Liposomes and EVs are studied more. Small-molecule delivery. Millard et al. used HUVEC EVs to deliver a photosensitizer and compared them to a 9:1 DPPC/DPPG liposomal formulation. [219] HT26 cells absorbed EVs faster than liposomes in 24 hours. EVs penetrated 3D spheroids deeper than liposomes. Schindler and colleagues studied DOX-vesicle uptake. [220] Myocet, Doxil, and HEK293 EVs were compared. HEK293 EVs were superior than liposomes at entering HEK293 cells. In cell line investigations, EV had the lowest IC50. Heusermann et al. compared EV absorption to 50:46:4 cationic lipid, cholesterol, and PEG-conjugated lipid. HEK293 liposomes grew as islands. After a few hours, the cell only took up a small fraction. EVs entered as single vesicles without accumulating at the cell surface. These studies suggest EVs may be taken up more efficiently than liposomal formulation. EV cargo delivery may improve. Sun and colleagues gave lipopolysaccharide-treated mice EVs containing curcumin. [222] Mice administered EVs had lower mortality than mice given liposomes with a same amount of curcumin, indicating EVs may be more efficient at delivering the medicine or have innate therapeutic effects. Extracellular vesicles (EVs) have one or more lipid membranes and contain all cell-internal and cell-surface chemicals. These include proteins, nucleic acids, and soluble

tiny molecules (such as second messengers, carbohydrates, and hormones). Figure 1 shows a schematic. EVs have captivated scientists in numerous fields because they can carry bioactive cargo between parental and acceptor cells. This cell may be near or far. Their lipidic barrier protects the signal from enzymatic breakdown and keeps it unadulterated. EV-mediated intercellular cargo transport is critical in physiological and pathological processes. 1 • Liquid biopsies are one biological application of EVs. Isolating these vesicles from physiological fluids would provide a snapshot of the producer cells at the time of vesicle-production, allowing near realtime monitoring of disease progression and therapeutic response, for example in cancer.

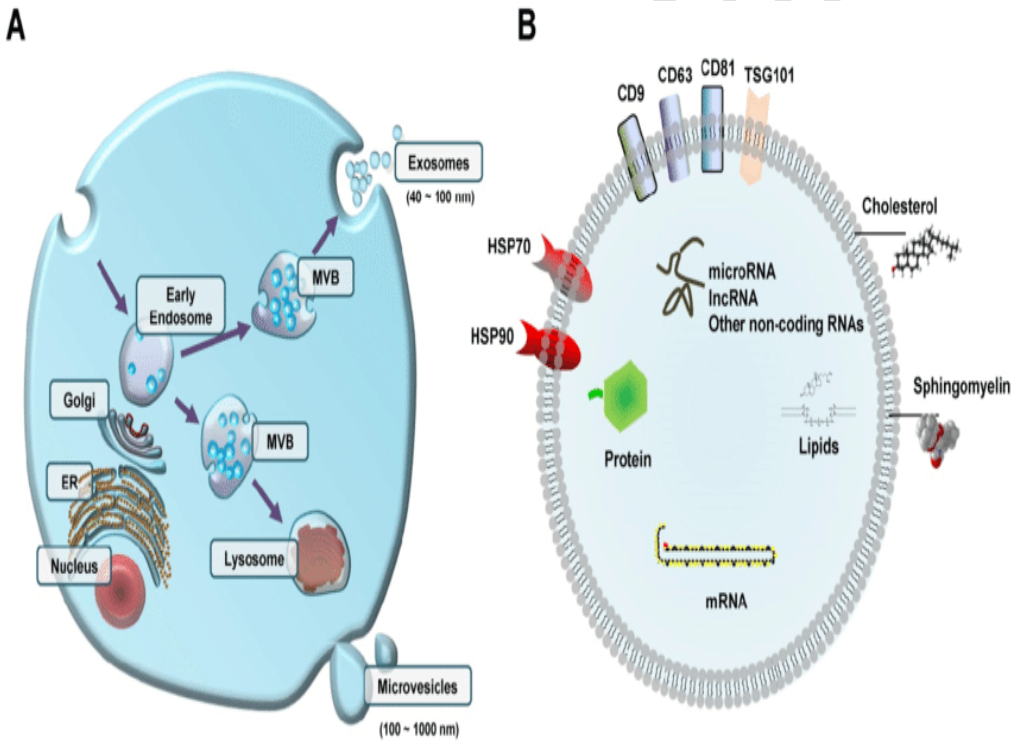

Fig: 4 Extracellular vesicle cargo (EVs). EVs are cell-derived nanosized vesicles that convey biological payload. They carry nucleic acids, lipids, and proteins. Surface molecules drive EV-

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environment interactions. EV contents may activate cellular pathways and cause phenotypic alterations after uptake by recipient cells.

ABC Phenomenon

Second and subsequent doses of some medications quickly clear the blood. Liposomes and lipid nanoparticles contain ABC (LNP). Humoral reactions to polyethylene glycol motifs have a role in clearance, but we still don't fully understand ABC and how to minimise its clinical impact. LNP are the most advanced mRNA delivery technology. This study studies mRNA-formulated LNP ABC in vivo and in vitro. ABC of mRNA-formulated LNP is dramatic and rapid because LNP can immediately activate B-1 cells, resulting in antiphosphorylcholine IgM Abs. Repeated injections activate B-2 cells, which create an anti-PEG antibody. ABC combines B-1 and B-2 responses to phosphorylcholine/LNP-encapsulated mRNA. PLD patients haven't shown ABC after multiple dosages. ABC may be caused by higher dosages (15 mol phospholipid/kg). This response may be connected to doxorubicin-mediated macrophage and B-cell apoptosis.

Liposomes for biomedical purpose

Liposome encapsulation can affect the geographical and temporal distribution of pharmaceutical molecules, minimising side effects and boosting therapeutic efficacy. Therapeutic and diagnostic uses of liposomes transporting drugs or other components, including their usage as a form, tool, or reagent in basic cell interface, recognition, and material action studies. Benefits and constraints of liposomal drug carriers depend on cell fate in vivo. Liposome-cell interactions in vitro and in vivo show adsorption or endocytosis. Rarely, membranes fuse. Cholesterol and fat interact with cell membrane components. In vivo liposomes are affected. Body has complex defences. Larger particles enter the bloodstream and cause thrombus formation, while immune system cells devour smaller particles, germs, and bacteria. This immune system response led to biocompatible and non-recognizable surfaces and confined micro particle drug carriers to targeting immune system cells. Natural liposomes. Spleen, liver, and bone marrow macrophages remove them.

Low sensitivity or specificity, pharmacological toxicity, and side effects hinder the diagnosis and treatment of many diseases, including cancer. The therapeutic dose of many drugs is close to the toxic dose. Temporal and geographical drug distribution can reduce toxicity.

Since the 1960s, liposomes have delivered drugs. They're biocompatible and biodegradable. Liposomes are natural nanocarriers. Nonphysiological chemicals can improve medicine delivery but are harmful.

Biocompatible liposomes can hold hydrophilic and hydrophobic drugs. A lipid bilayer protects a drug from enzymatic, immunologic, and chemical degradation. Liposomes protect medications from being digested and reduce exposure to healthy tissue during blood circulation. Both increase TI. Cytotoxic drugs are given in large doses to the tumour site. Encapsulated medications have fewer side effects. lipid bilayer, drug size, oil/water partition coefficient, and lipid membrane interactions affect medication delivery. The type and density of liposome surface charge influence liposome delivery (-potential).

Polarity and partition coefficient determine a molecule's liposomal encapsulation and placement. Hydrophobic medications dwell in the liposome's acyl hydrocarbon chain; encapsulation depends on chain length and packing density. Changing drug-to-lipid ratio affects hydrophobic molecule encapsulation. Polar/hydrophilic medications localise in the aqueous core or water–lipid interface, near the liposome's polar head groups. Drug-to-lipid ratio doesn't affect encapsulation efficiency. Hydrophilic liposome chains prefer hydrophilic entrapment. 51

Bioavailable liposomal medicines are released. Optimizing the release rate of a liposome-vehicle drug is critical to stay within its therapeutic window. Prevent drug release. Scientists have changed lipid bilayers or entrapped drugs to solve this problem. Adding cholesterol or sphingomyelin to liposomes improves cargo retention. 52–54 To control release rate, use drugs with qualities that promote lipid nanovector retention. Liposomes are permeable to hydrophobic drugs but not biomembranes. Liposomes release hydrophilic anticancer drugs over hours to days. 55,56 Hydrophobic medicines are easily liberated from lipid bilayer fatty acyl chains. Highly hydrophobic drugs, like paclitaxel, are hard to keep in liposomes. Their formulations and pharmacokinetics have been studied. 57

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Intermediate-solubility anticancer drugs partition readily between the liposome bilayer and exterior or interior water phase, resulting in fast liposomal release. Changing the liposomes' interior pH or creating molecular complexes can improve retention of weak bases like Dox or Dauno. 58,59 Boosting precipitation or encapsulating polyanions like dextran sulphate can increase drug retention. 60,61 Docetaxel can be converted to a liposomal weak-base prodrug. 62

Liposomes should store, maintain, and deliver drugs well. These features could improve biopharmaceutical profile by reducing toxicity, improving pharmacokinetics, and increasing therapeutic index. Liposomes may be superior to conventional dosage forms for parenteral, topical, and pulmonary delivery.

Clinical research show liposomal encapsulation changes drug toxicity. Liposomal drugs enhanced patient outcomes by reducing cardiotoxicity, nausea, and vomiting. 63,64 Liposomal vincristine improved its therapeutic efficacy. Vincristine sulfate-liposome injection increased therapeutic index by permitting dose intensification. This is because free vincristine sulphate has a lower clearance and a higher AUC. 65 Amphotericin B liposomal is a superior antibacterial. Liposomal amphotericin B treats histoplasmosis and AIDS (AIDS). 66 pH-sensitive liposomes containing nystatin boosted mouse anticryptococcal efficacy. 67

Dox, daunorubicin, and epirubicin encase tumours. Liposomal anthracyclines reduced cardiotoxicity compared to free drugs. 68,69 Meta-analysis compared liposomal Dox to anthracyclines. Both liposomal Dox and PEGylated liposomal Dox (PLD) had favourable toxicity profiles, with better cardiac safety and less myelosuppression, alopecia, nausea, and vomiting than conventional anthracyclines, making them a good choice for elderly patients, those with cardiac disease risk factors, and those who had previously used anthracyclines. 70

PLD's innovative formulation increases intratumor accumulation and prolongs drug circulation. Standard ovarian cancer treatment includes PLD (extensively reviewed in Pisano et al). 71

Several Phase II trials with PLD in platinum-resistant ovarian cancer patients reported 10–20% objective response rates. 72–74 50% of patients suffered palmar–plantar erythrodysesthesia, toxic acral erythema, and mucositis. Palmar–plantar erythrodysesthesia causes dose decrease and treatment cessation. PLD formulation is safer for cardiac toxicity than Dox. 77 Most PLD studies showed a lower incidence of cardiac failure even at doses over 500 mg/m2 compared to Dox (7.5% at 400–550 mg/m2). 78–80 In a prospective experiment on patients with advanced gynaecological malignancies treated with PLD, endomyocardial biopsies demonstrated minimal cardiac damage (median PLD dose 708 mg/m2). 81 PLD's cardiac safety allows extended treatment. Phase II results in AIDS-related Kaposi's sarcoma patients treated with PLD are favourable. In metastatic breast cancer patients, doses above 450 mg/m2 did not reduce left ventricular ejection fraction. 80 A relapsed ovarian cancer patient on PLD maintenance medication for more than a year had no cardiac events.

Conclusion

Nanotechnology is an interdisciplinary science where chemists, physicists, biologists, and pharmaceutical scientists have all played key roles. Nontechnology in medication delivery and medicine has created several avenues for customising and safer treatment options, as this overview shows. Nanotechnology has advanced cancer, HIV/AIDS, non-invasive imaging, and nutraceutical delivery. Researchers can deliver medications for longer periods of time with less frequent doses (sustained release) and with improved precision and penetration in hard-to-reach tissues by manipulating molecule size and surface characteristics.

COMPETING INTERESTS DISCLAIMER:

Authors have declared that no competing interests exist. The products used for this research are commonly and predominantly use products in our area of research and country. There is absolutely no conflict of interest between the authors and producers of the products because we do not intend to use these products as an avenue for any litigation but for the advancement of knowledge. Also, the research was not funded by the producing company rather it was funded by personal efforts of the authors.

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