



Liposome Nano-particles for Therapeutic and Diagnostic Applications

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Authors' contributions

This work was carried out in collaboration among all authors. All authors read and approved the final manuscript.

Article Information

DOI: 10.9734/JAMMR/2022/v34i2031475

Open Peer Review History:

This journal follows the Advanced Open Peer Review policy. Identity of the Reviewers, Editor(s) and additional Reviewers, peer review comments, different versions of the manuscript, comments of the editors, etc are available here: <https://www.sdiarticle5.com/review-history/88038>

Review Article

Received 15 April 2022
Accepted 22 June 2022
Published 11 July 2022

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.

Keywords: *Liposome nanoparticles; combination therapy; controlled drug delivery system; nanostructure.*

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1. 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, dipalmitoyl phosphatidylcholine). 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 [1]. Most liposomes are cylindrical, with sizes of 30 nm to several micrometres. 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 [2].

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 [3-5].

Due to their low toxicity, biocompatibility, biodegradability, and ability to trap hydrophilic and lipophilic medications, liposomes have gained favour as a drug delivery device [6,7]. Liposomes can minimise medicine toxicity and/or target specific cells [8-10].

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 [11].

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 [12].

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

1.1 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). 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, 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.

1.2 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).

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 defense 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.

STRUCTURAL CLASSIFICATION OF LIPOSOMES:

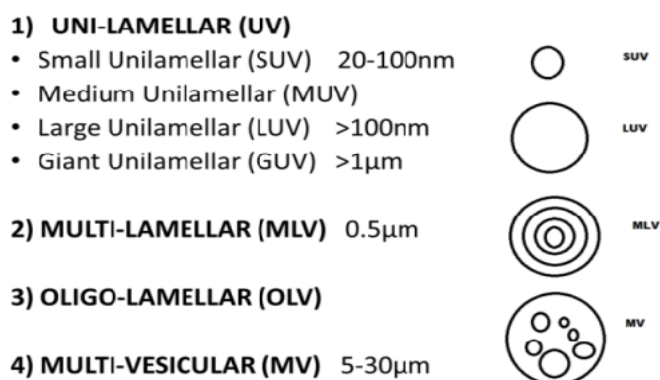


Fig. 1. Classification of Liposomes

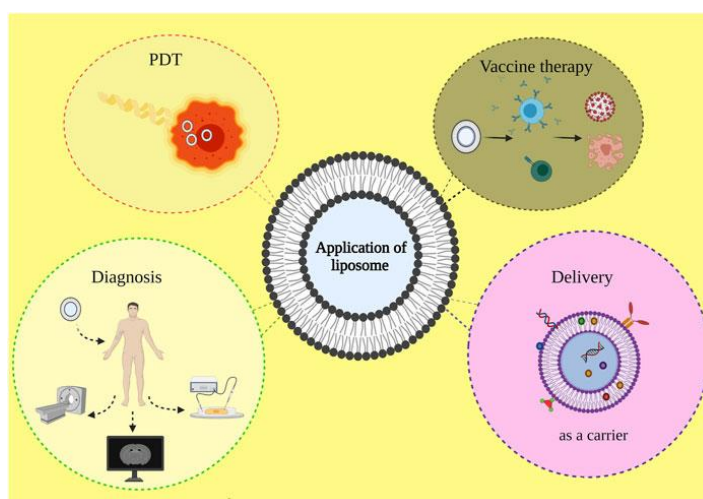


Fig. 2. Liposomes biological Application

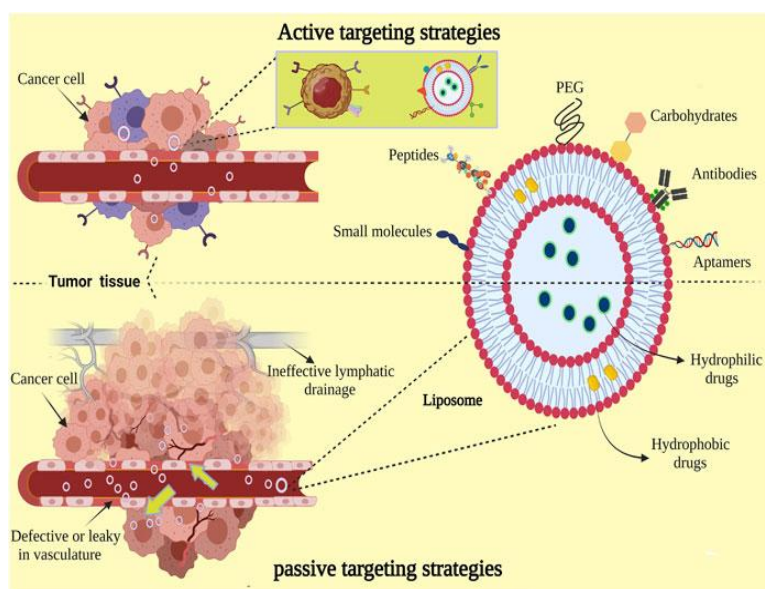


Fig. 3. Targeting passively and actively

Liposomes have been widely explored in drug delivery to malignant and tumour tissues via passive and active targeting (Fig. 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.

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.

2. METHODS FOR PREPARATION LIPOSOMES

2.1 Thin Film 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.

2.2 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.

2.3 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.

2.4 Pharmacological Difficulties Liposomal Delivery Systems

The field of delivery methods for medicinal agents or natural-based active chemicals has recently undergone substantial advancements [13,14] 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.

2.5 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 ^{99m}Tc-labeled nanoalbumin microcolloid from blood. This approach detects granulopetic activity and efficiency. The granulopetic index of the RES clearance curve was exponential. Liver, spleen, and bone marrow cells absorbed ^{99m}Tc-labeled nanoalbumin 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 [15,16]. 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.

2.6 Oponins 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. HT26 cells absorbed EVs faster than liposomes in 24 hours. EVs penetrated 3D spheroids deeper than liposomes. Schindler and colleagues studied DOX-vesicle uptake. 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. 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). Fig. 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 [17-21].

EVs are cell-derived nanosized vesicles that convey biological payload. They carry nucleic acids, lipids, and proteins. Surface molecules drive EV-environment interactions. EV contents may activate cellular pathways and cause phenotypic alterations after uptake by recipient cells.

2.7 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.

2.8 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 [22-26]. 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 [27-29].

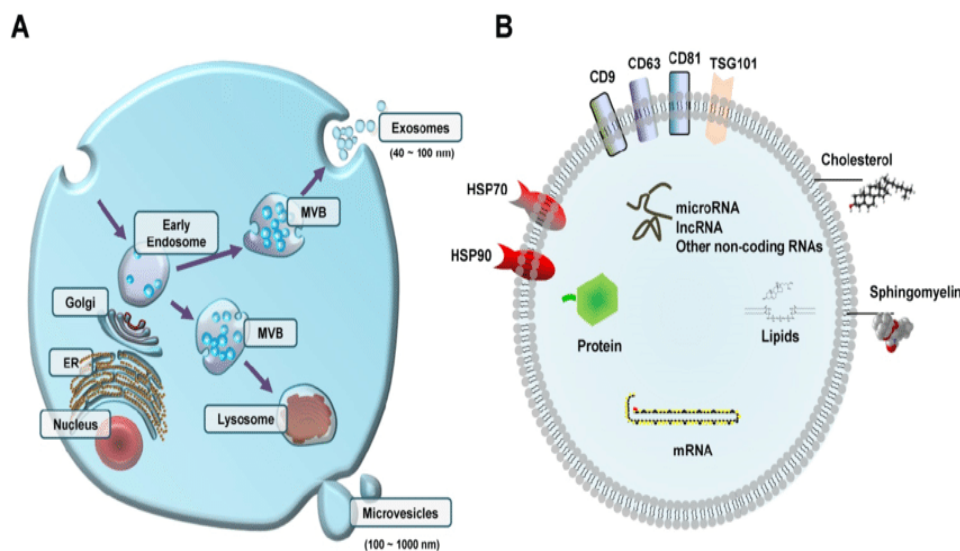


Fig. 4. Extracellular vesicle cargo (EVs)

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 [30-39].

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 [40-43]. 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 [44].

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 [45-48]. Scientists have changed lipid bilayers or entrapped drugs to solve this problem. Adding cholesterol or sphingomyelin to liposomes improves cargo retention [49-51]. 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 [52,53]. 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 [54].

Intermediate-solubility anticancer drugs partition readily between the liposome bilayer and exterior or interior water phase, resulting in fast liposomal release [55-59]. Changing the liposomes' interior pH or creating molecular complexes can improve retention of weak bases like Dox or Dauno [60,61]. Boosting precipitation or encapsulating polyanions like dextran sulphate can increase drug retention [62,63]. Docetaxel can be converted to a liposomal weak-base prodrug [64].

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 [65,66]. 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 [67]. 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 [68].

Dox, daunorubicin, and epirubicin encase tumours. Liposomal anthracyclines reduced cardiotoxicity compared to free drugs [69,70]. 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 [71].

PLD's innovative formulation increases intratumor accumulation and prolongs drug circulation. Standard ovarian cancer treatment includes PLD (extensively reviewed in Pisano et al) [72]. Several Phase II trials with PLD in platinum-resistant ovarian cancer patients reported 10-20% objective response rates [73-

75]. 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 [76]. 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) [77–79]. 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). 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 [79]. A relapsed ovarian cancer patient on PLD maintenance medication for more than a year had no cardiac events.

3. CONCLUSION

Nanotechnology is an interdisciplinary science where chemists, physicists, biologists, and pharmaceutical scientists have all played key roles. Nanotechnology 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.

CONSENT

It is not applicable.

ETHICAL APPROVAL

It is not applicable.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

REFERENCES

1. Scheidt HA, Pampel A, Nissler L, Gebhardt R, Huster D. Investigation of the membrane localization and distribution of flavonoids by high-resolution magic angle

- spinning NMR spectroscopy. *BBA Biomembr.* 2004;1663:97–107. DOI: 10.1016/j.bbamem.2004.02.004
2. Tammela P, Laitinen L, Galkin A, Wennberg T, Heczko R, Vuorela H, Slotte JP, Vuorela P. Permeability characteristics and membrane affinity of flavonoids and alkyl gallates in Caco-2 cells and in phospholipid vesicles. *Arch. Biochem. Biophys.* 2004;425:193–199. DOI: 10.1016/j.abb.2004.03.023
3. Hendrich AB. Flavonoid-membrane interactions: Possible consequences for biological effects of some polyphenolic compounds. *Acta Pharmacol. Sin.* 2006; 27:27–40. DOI: 10.1111/j.1745-7254.2006.00238.x
4. Roshan K, Priya damwani, Shivam kumar, Adarsh suman, Suthar Usha. An overview on health benefits and risk factor associated with coffee. *International Journal Research and Analytical Review.* 2020;7(2):237-249.
5. Siontorou CG, Nikoleli GP, Nikolelis DP, Karapetis SK. Artificial Lipid Membranes: Past, Present, and Future. *Membranes.* 2017;7:38. DOI: 10.3390/membranes7030038.
6. Negri A, Naponelli V, Rizzi F, Bettuzzi S. Molecular Targets of Epigallocatechin—Gallate (EGCG): A Special Focus on Signal Transduction and Cancer. *Nutrients.* 2018;10:1936. DOI: 10.3390/nu10121936
7. Hoffman JF. Physiological characteristics of human red blood cell ghosts. *J. Gen. Physiol.* 1958;42:9–28. DOI: 10.1085/jgp.42.1.9
8. Simons TJ. The preparation of human red cell ghosts containing calcium buffers. *J. Physiol.* 1976;256:209–225. DOI: 10.1113/jphysiol.1976.sp011321
9. Giess F, Friedrich MG, Heberle J, Naumann RL, Knoll W. The protein-tethered lipid bilayer: A novel mimic of the biological membrane. *Biophys. J.* 2004;87: 3213–3220. DOI: 10.1529/biophysj.104.046169.
10. Movileanu L, Neagoe I, Flonta ML. Interaction of the antioxidant flavonoid quercetin with planar lipid bilayers. *Int. J. Pharmaceut.* 2000;205:135–146. DOI: 10.1016/S0378-5173(00)00503-2
11. Sahana S, Purabi saha, Roshan kumar, Pradipta das, Indranil Chatterjee, Prasit Roy, Sk Abdur Rahamat. A Review of the 2019 Corona virus (COVID-19) World

- Journal of Pharmacy and Pharmaceutical Science. 2020; 9(9):2367-2381.
12. Peetla C, Stine A, Labhasetwar V. Biophysical interactions with model lipid membranes: Applications in drug discovery and drug delivery. *Mol. Pharmaceut.* 2009;6:1264–1276. DOI: 10.1021/mp9000662
 13. Charcosset C, Juban A, Valour JP, Urbaniak S, Fessi H. Preparation of liposomes at large scale using the ethanol injection method: Effect of scale-up and injection devices. *Chem. Eng. Res. Des.* 2015;94:508–515. DOI: 10.1016/j.cherd.2014.09.008
 14. Pham HL, Shaw PN, Davies NM. Preparation of immuno-stimulating complexes (ISCOMs) by ether injection. *Int. J. Pharmaceut.* 2006;310:196–202. DOI: 10.1016/j.ijpharm.2005.11.011
 15. Kumar R, Saha P, Kumar Y, Sahana S, Dubey A, Prakash O. A review on diabetes mellitus: Type 1 & type 2; 2020.
 16. Dubey A, Yadav P, Verma P, Umar R. Investigation of Proapoptotic Potential of Ipomoea carnea Leaf Extract on Breast Cancer Cell Line. *Journal of Drug Delivery and Therapeutics.* 2022;12(1):51-55.
 17. Ishida T, Kirchmeier MJ, Moase EH, Zalipsky S, Allen TM. Targeted delivery and triggered release of liposomal doxorubicin enhances cytotoxicity against human B lymphoma cells. *Biochim. Biophys. Acta.* 2001b; 1515:144–158. DOI: 10.1016/S0005-2736(01)00409-6
 18. Saha P, Kumar R, Nyarko RO, Kahwa I, Owusu P. Herbal secondary metabolite for gastro-protective ulcer activity with api structures; 2021.
 19. Ishida T, Masuda K, Ichikawa T, Ichihara M, Irimura K, Kiwada H. Accelerated clearance of a second injection of PEGylated liposomes in mice. *Int. J. Pharm.* 2003;255:167–174. DOI: 10.1016/S0378-5173(03)00085-1
 20. Mukesh Kr. Singh, Ajay Kumar, Roshan Kumar P. Satheesh Kumar, Selvakumar P, Anurag Chourasia. Effects of Repeated Deep Frying on Refractive Index and Peroxide Value of Selected Vegetable Oils. *International Journal for Research in Applied Sciences and Biotechnology.* 2022;9(3):28–31. Available:<https://doi.org/10.31033/ijrasb.9>
 21. Kumar R, Saha P, Sarkar S, Rawat N, Prakash A. A REVIEW ON NOVEL DRUG DELIVERY SYSTEM. *IJRAR-International Journal of Research and Analytical Reviews (IJRAR).* 2021;8(1):183-199.
 22. Zhu Y, Yu JN, Tong SS, Wang L, Peng M, Cao X, et al. Preparation and in vitro evaluation of povidone-sodium cholate-phospholipid mixed micelles for the solubilization of poorly soluble drugs. *Arch Pharm Res.* 2010;33:911–7
 23. Bind A, Das S, Singh VD, Kumar R, Chourasia A, Saha P. Natural bioactives for the potential management of gastric ulceration. *Turkish Journal of Physiotherapy and Rehabilitation.* 32;3.
 24. Du B, Li Y, Li XT A YM, Chen CQ, Zhang ZZ. Preparation, characterization and *in vivo* evaluation of 2-methoxyestradiol-loaded liposomes. *Int J Pharm.* 2010; 384:140–7.
 25. Hua S, Marks E, Schneider JJ, Keely S. Advances in oral nano-delivery systems for colon targeted drug delivery in inflammatory bowel disease: selective targeting to diseased versus healthy tissue. *Nanomedicine.* 2015;11:1117–1132. DOI: 10.1016/j.nano.2015.02.018
 26. Hua S, Wu SY. The use of lipid-based nanocarriers for targeted pain therapies. *Front. Pharmacol.* 2013; 4:143. DOI: 10.3389/fphar.2013.00143
 27. Immordino ML, Dosio F, Cattel L. Stealth liposomes: review of the basic science, rationale, and clinical applications, existing and potential. *Int. J. Nanomedicine.* 2006; 1:297–315.
 28. Ishida T, Ichihara M, Wang X, Kiwada H. Spleen plays an important role in the induction of accelerated blood clearance of PEGylated liposomes. *J. Control. Release.* 2006a;115:243–250. DOI: 10.1016/j.jconrel.2006.08.001
 29. Ishida T, Ichihara M, Wang X, Yamamoto K, Kimura J, Majima E, et al. Injection of PEGylated liposomes in rats elicits PEG-specific IgM, which is responsible for rapid elimination of a second dose of PEGylated liposomes. *J. Control. Release.* 2006b; 112:15–25. DOI: 10.1016/j.jconrel.2006.01.005
 30. Dua JS, Rana PA, Bhandari DK. Liposome: Methods of preparation and applications. *Int. J. Pharm. Stud. Res.* 2012;3:14–20.
 31. Abram V, Berlec B, Ota A, Šentjurc M, Blatnik P, Ulrih NP. Effect of flavonoid structure on the fluidity of model lipid

- membranes. *Food Chem.* 2013;139:804–813.
DOI: 10.1016/j.foodchem.2013.01.100.
32. Weissig V. *Liposomes: Methods and Protocols: Pharmaceutical Nanocarriers*. Volume 1. Humana Press (Springer Science+Business Media); New York, NY, USA. 2010;564.
 33. Elhissi AM, O'Neill MA, Roberts SA, Taylor KM. A calorimetric study of dimyristoylphosphatidylcholine phase transitions and steroid-liposome interactions for liposomes prepared by thin film and proliposome methods. *Int. J. Pharmaceut.* 2006;320:124–130.
DOI: 10.1016/j.ijpharm.2006.04.015
 34. Isailović BD, Kostić IT, Zvonar A, Đorđević VB, Gašperlin M, Nedović VA, Bugarski BM. Resveratrol loaded liposomes produced by different techniques. *Innov. Food Sci. Emerg.* 2013;19:181–189.
DOI: 10.1016/j.ifset.2013.03.006
 35. Jovanović AA, Balanč BD, Ota A, Ahlin Grabnar P, Djordjević VB, Šavikin KP, Bugarski BM, Nedović VA, Poklar Ulrih N. Comparative Effects of Cholesterol and β -Sitosterol on the Liposome Membrane Characteristics. *Eur. J. Lipid Sci. Tech.* 2018;120:1800039.
DOI: 10.1002/ejlt.201800039
 36. Ota A, Abramovič H, Abram V, Poklar Ulrih N. Interactions of p-coumaric, caffeic and ferulic acids and their styrenes with model lipid membranes. *Food Chem.* 2011;125:1256–1261.
DOI: 10.1016/j.foodchem.2010.10.054
 37. Lasch J, Weissig V, Brandl M. Preparation of liposomes. In: Torchilin V.P., Weissig V., editors. *Liposomes—A Practical Approach*. 2nd ed. Oxford University Press; New York, NY, USA: 2003;3–30.
 38. Sahana S, Roshan kumar, Sourav nag, Reshmi paul, Nilayan guha, Indranil Chatterjee. A Review on Alzheimer disease and future prospects. *World Journal of Pharmacy and Pharmaceutical Science.* 2020; 9(9):1276-1285.
 39. Ishikawa H, Shimoda Y, Matsumoto K. Preparation of liposomal microcapsules by proliposome method with soybean lecithin. *J. Fac. Agric.* 2004;49:119–127.
 40. Lasic DD, Papahadjopoulos D. *Medical Applications of Liposomes*. Elsevier Science Publishers B. V.; Amsterdam, The Netherlands.1998;779.
 41. Awuchi CG, Amagwula IO, Priya P, Kumar R, Yezdani U, Khan MG. Aflatoxins in foods and feeds: A review on health implications, detection, and control. *Bull. Environ. Pharmacol. Life Sci.* 2020; 9:149-155.
 42. Chebil L, Humeau C, Anthoni J, Dehez F, Engasser JM, Ghoul M. Solubility of Flavonoids in Organic Solvents. *J. Chem. Eng. Data.* 2007;52:1552–1556.
DOI: 10.1021/je7001094
 43. Bangham AD, Hill MW, Miller NGA. Preparation and use of liposomes as models of biological membranes. In: Korn E.D., editor. *Methods in Membrane Biology*. Volume 1. Springer; Boston, MA, USA: 1974;1–68.
 44. Jaafar-Maalej C, Elaissari A, Fessi H. Lipid-based carriers: Manufacturing and applications for pulmonary route. *Expert Opin. Drug Deliv.* 2012;9:1111–1127.
DOI: 10.1517/17425247.2012.702751
 45. Elhissi A, Gill H, Ahmed W, Taylor K. Vibrating-mesh nebulization of liposomes generated using an ethanol-based proliposome technology. *J. Lipos. Res.* 2011;21:173–180.
DOI: 10.3109/08982104.2010.505574
 46. Istenič K, Cerc Korošec R, Poklar Ulrih N. Encapsulation of (-)- epigallocatechin gallate into liposomes and into alginate or chitosan microparticles reinforced with liposomes. *J. Sci. Food Agric.* 2016;96: 4623–4632.
DOI: 10.1002/jsfa.7691
 47. Nyarko RO, Kumar R, Sharma S, Chourasia A, Roy A, Saha P. Antibacterial activity of herbal plant-tinospora cordifolia and catharthus roseus; 2022.
 48. Torchilin VP, Weissig V. *Liposomes—A Practical Approach*. 2nd ed. Oxford University Press; Oxford, UK. 2003; 369.
 49. Jahn F, Jordan K, Behlendorf T, Globig C, Schmoll HJ, Müller-Tidow C, et al. Safety and efficacy of liposomal cytarabine in the treatment of neoplastic meningitis. *Oncology.* 2015;89:137–142.
DOI: 10.1159/000380913
 50. Kirpotin DB, Drummond DC, Shao Y, Shalaby MR, Hong K, Nielsen UB, et al. Antibody targeting of long-circulating lipidic nanoparticles does not increase tumor localization but does increase internalization in animal models. *Cancer Res.* 2006;66:6732–6740.
DOI: 10.1158/0008-5472.CAN-05-4199
 51. Kirpotin D, Park JW, Hong K, Zalipsky S, Li WL, Carter P, et al. Sterically stabilized anti-HER2 immunoliposomes: design and

- targeting to human breast cancer cells in vitro. *Biochem. Mosc.* 1997; 36:66–75.
DOI: 10.1021/bi962148u
52. Klimuk SK, Semple SC, Scherrer P, Hope MJ. Contact hypersensitivity: a simple model for the characterization of disease-site targeting by liposomes. *Biochim. Biophys. Acta.* 1999;1417:191–201.
DOI: 10.1016/S0005-2736(98)00261-2
 53. Koning GA, Storm G. Targeted drug delivery systems for the intracellular delivery of macromolecular drugs. *Drug Discov. Today.* 2003;8:482–483.
DOI: 10.1016/S1359-6446(03)02699-0
 54. Sahana S, Kumar R, Nag S, Paul R, Chatterjee I, Guha N. A review on alzheimer disease and future prospects; 2020.
 55. Jaafar-Maalej C, Diab R, Andrieu V, Elaissari A, Fessi H. Ethanol injection method for hydrophilic and lipophilic drug-loaded liposome preparation. *J. Lipos. Res.* 2010;20:228–243.
DOI: 10.3109/08982100903347923.
 56. Pons M, Foradada M, Estelrich J. Liposomes obtained by the ethanol injection method. *Int. J. Pharmaceut.* 1993;95:51–56.
DOI: 10.1016/0378-5173(93)90389-W
 57. Kumar R, Saha P, Lokare P, Datta K, Selvakumar P, Chourasia A. A Systemic Review of *Ocimum sanctum* (Tulsi): Morphological Characteristics, Phytoconstituents and Therapeutic Applications. *International Journal for Research in Applied Sciences and Biotechnology.* 2022; 9(2):221-226.
 58. Xiao YY, Song YM, Chen ZP, Ping QN. The preparation of silybin-phospholipid complex and the study on its pharmacokinetics in rats. *Int J Pharm.* 2006;307:77–82.
 59. Yu JN, Zhu Y, Wang L, Peng M, Tong SS, Cao X, et al. Enhancement of oral bioavailability of the poorly water-soluble drug silybin by sodium cholate/phospholipid-mixed micelles. *Acta Pharmacol Sin.* 2010;31:759–64.
 60. Kraft JC, Freeling JP, Wang Z, Ho RJ. Emerging research and clinical development trends of liposome and lipid nanoparticle drug delivery systems. *J. Pharm. Sci.* 2014;103:29–52.
DOI: 10.1002/jps.23773
 61. Kunstfeld R, Wickenhauser G, Michaelis U, Teifel M, Umek W, Naujoks K, et al. Paclitaxel encapsulated in cationic liposomes diminishes tumor angiogenesis and melanoma growth in a “humanized” SCID mouse model. *J. Invest. Dermatol.* 2003;120:476–482.
DOI: 10.1046/j.1523-1747.2003.12057.x
 62. Kumar R, Dubey A. Phytochemical investigation and hepatoprotective evaluation acacia rubica extract isonized and paracetamol induced animal toxicity. *Turkish Journal of Physiotherapy and Rehabilitation.* 32;3.
 63. Laverman P, Boerman OC, Oyen WJ, Dams ET, Storm G, Corstens FH. Liposomes for scintigraphic detection of infection and inflammation. *Adv. Drug Deliv. Rev.* 1999;37:225–235.
 64. Laverman P, Carstens MG, Storm G, Moghimi SM. Recognition and clearance of methoxypoly(ethyleneglycol)2000-grafted liposomes by macrophages with enhanced phagocytic capacity. Implications in experimental and clinical oncology. *Biochim. Biophys. Acta.* 2001;1526:227–229.
DOI:10.1016/S0304-4165(01)00142-8
 65. Löhr JM, Haas SL, Bechstein WO, Bodoky G, Cwiertka K, Fischbach W, et al. Cationic liposomal paclitaxel plus gemcitabine or gemcitabine alone in patients with advanced pancreatic cancer: a randomized controlled phase II trial. *Ann. Oncol.* 2012;23:1214–1222.
DOI: 10.1093/annonc/mdr379
 66. Nyarko RO, Prakash A, Kumar N, Saha P, Kumar R. Tuberculosis a globalized disease. *Asian Journal of Pharmaceutical Research and Development.* 2021; 9(1):198-201.
 67. Lyass O, Uziely B, Ben-Yosef R, Tzemach D, Heshing NI, Lotem M, et al. Correlation of toxicity with pharmacokinetics of pegylated liposomal doxorubicin (Doxil) in metastatic breast carcinoma. *Cancer.* 2000;89:1037–1047.
DOI:10.1002/10970142(20000901)89:5<1037::AID-CNCR13>3.0.CO;2-Z
 68. Maruyama K. PEG-immunoliposome. *Biosci. Rep.* 2002;22:251–266.
DOI: 10.1023/A:1020138622686
 69. Metselaar JM, Storm G. Liposomes in the treatment of inflammatory disorders. *Expert Opin. Drug Deliv.* 2005;465–76.
DOI: 10.1517/17425247.2.3.465
 70. Raj A, Tyagi S, Kumar R, Dubey A, Hourasia AC. Effect of isoproterenol and thyroxine in herbal drug used as cardiac

- hypertrophy. Journal of Cardiovascular Disease Research. 2021;204-217.
71. Moghimi SM, Hunter AC. Capture of stealth nanoparticles by the body's defences. Crit. Rev. Ther. Drug Carrier Syst. 2001;18:527–550. DOI:10.1615/CritRevTherDrugCarrierSyst.v18.i6.30
72. Moghimi SM, Szebeni J. Stealth liposomes and long circulating nanoparticles: critical issues in pharmacokinetics, opsonization and protein-binding properties. Prog. Lipid Res. 2003;42:463–478. DOI: 10.1016/S0163-7827(03)00033-X
73. Monteiro N, Martins A, Reis RL, Neves NM. Liposomes in tissue engineering and regenerative medicine. J. R. Soc. Interface. 2014;11:20140459. DOI: 10.1098/rsif.2014.0459
74. Purabisaha RK, Rawat SSN, Prakash A. A review on novel drug delivery system; 2021.
75. Narang AS, Chang RK, Hussain MA. Pharmaceutical development and regulatory considerations for nanoparticles and nanoparticulate drug delivery systems. J. Pharm. Sci. 2013;102:3867–3882. DOI: 10.1002/jps.23691
76. Nehoff H, Parayath NN, Domanovitch L, Taurin S, Greish K. Nanomedicine for drug targeting: strategies beyond the enhanced permeability and retention effect. Int. J. Nanomedicine. 2014; 9:2539–2555. DOI: 10.2147/IJN.S47129
77. Ning YM, He K, Dagher R, Sridhara R, Farrell AT, Justice R, et al. Liposomal doxorubicin in combination with bortezomib for relapsed or refractory multiple myeloma. Oncology (Williston Park). 2007; 21:1503–1508. Discussion: 11, 13, 16 passim.
78. Safi SZ, Qvist R, Kumar S, Ismail ISB. Molecular mechanisms of Diabetic Retinopathy, general preventive strategies and novel therapeutic targets. Experimental and Clinical Endocrinology & Diabetes. 2013;121(03):P109.
79. Northfelt DW, Martin FJ, Working P, Volberding PA, Russell J, Newman M, et al. Doxorubicin encapsulated in liposomes containing surface-bound polyethylene glycol: Pharmacokinetics, tumor localization, and safety in patients with AIDS-related Kaposi's sarcoma. J. Clin. Pharmacol. 1996;36:55–63. DOI: 10.1002/j.1552-4604.1996.tb04152.x

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