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Recent progress in synthesis of nano based liposomal drug delivery systems: A glance to their medicinal applications

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ABSTRACT

The process of providing a pharmaceutical substance with a therapeutic effect in human or animals is known as drug delivery. There are several prospects to detect, treat, and heal of difficult illnesses for the development of nanoparticle-based medicines. A diversity of nanomaterials may be transformed into intelligent systems with discreet medicinal and imaging agents by manipulating their size, shape, surface modification, surface features, and materials employed. Such nanomaterials can show controlled release treatment by delivering medications to particular tissues. Additionally, a number of drug delivery methods based on liposomes have been developed as medical treatments. Improvements in the diagnosis and treatment of illnesses have been facilitated using nanoparticles as a tool. Tailored and extended medication administration based liposomal nanostructures improves patient compliance with less frequent doses while reducing drug-related damage. The most current developments in nanostructures synthesis for drug delivery and treatments with emphasis on liposomes are highlighted in this work. Because of their excellent biocompatibility, biodegradability, and minimal immunogenicity, liposomes are the most widely employed nanocarriers for a variety of hydrophobic and hydrophilic compounds that may be biologically operative. Additionally, liposomes have shown to improve the drug dissolution rate, regulated drug delivery, and ability to modify their surface. Liposomes have developed from traditional and immunological liposomes to stimuli-responsive and actively targeted liposomes based on their formation. To treat a variety of disorders, various liposomal-based drug delivery systems are presently medically licensed; therefore, in this review, the structure, content, production techniques, and some therapeutic uses of liposomes are addressed.

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1. Introduction

By regulating the rate, duration, and location of medication release in the body, a drug delivery system makes it possible to administer a therapeutic material into the body and increases its safety and effectiveness. Administering drugs at regulated rates, slowly and specifically are some of the alluring strategies to potentially solve difficulties with traditional administration of drugs, Tiwari et al. (2012), Misra et al. (1997) and Mukhopadhyay et al. (1995). A wider insight of the pharmacokinetic (pk) and pharmacodynamic (pd) concepts underlying the progression of novel drugs as well as control the activity and administration of powerful opioid analgesics, inhalation anesthetics, sedative/hypnotics, and muscle relaxants has been made possible by various studies, Kumar et al. (2010). New devices, ideas, and methods known as controlled-release technology (CRT), such as transdermal and transmucosal controlled-release administration systems have emerged as a result of identical advancements with other substances, Leppert et al. (2018). There has been a drop in the entrance of novel chemical species as a consequence of increasing research and development expenses, fewer companies performing pharmaceutical research and degradation of effective patent life. Due to the application of nanotechnology especially nanomedicine in the fields of health and medicine including imaging, sensing, tailored drug, gene deliveries and artificial implants, it has received a great deal of attention, Ali et al. (2015) and Andrews et al. (2013). Recent publications have highlighted cutting-edge medications created from nanomaterials to treat cancer and eradicate numerous human infections therefore, nanomedicine has been recently used to describe the application of nanomaterials in the therapy, detection, tracking, and management of illnesses especially when creating new drugs, Pawar et al. (2018).

Drug delivery systems (DDSs) are one of the possible uses for nanotechnology in the diagnosis, cure, and protection of several illnesses. The creation of medication delivery systems based on nanoparticles has increased our ability to diagnose and treat difficult illnesses, Dhal et al. (2020) and Byrne et al. (2018). Drug delivery to specific areas of the human body is now possible using the nanomaterials modifications. These microscopic structures can also be used to monitor drug aggregation and metabolism in cells or tissues to a better recognize the pk and pd of a given medication, Jafari et al. (2012). Because of their small size, nanostructures may pass easily into cells via engaging with particular biological constituents, allowing for specific targeting and deposition in particular cells or tissues. They are also pH-sensitive entities that can quickly lose their functionality, destabilize or breakdown at low pH in a cell to liberate medication dosage, Koocheki et al. (2009). Formulating the appropriate nano-based DDSs just a few years ago demonstrates a considerable function in nanomedicine for the screening and therapy of cancer, cardiovascular system diseases, respiratory, blood, and neurological problems, diabetes, inflammatory/infectious diseases, Parkinson's or Alzheimer's disease and orthopedic issues, Xia et al. (2006). In DDSs the use of nanosized technology in the development of pharmaceuticals with poor water solubility has grown significantly. Moreover, nanosized pharmaceuticals have a lower effective dose, less fed/fasted variation, improved dissolution rate, better oral bioavailability, more extensive surface area and quicker time of performing, Liu and Park (2010) and Sebaaly et al. (2015). In fact, by lowering the particle size to the nanometer level, the bioavailability and dissolution rate improve due to the improve in surface area. It is possible for nanomaterials employed in DDSs to survive for weeks or longer without degrading in the microfluidic context of a cell. for instance, Carbon nanotubes (CNTs) can last for a prolonged duration. Nanoparticle-based DDSs are non-immunogenic while introducing to the organism as they are consistent with the immune system and thus do not cause an immunological reaction, Gortzi et al. (2007), Gibis et al. (2014) and Jahangirian et al. (2017).

2. Nanotechnology in drug delivery

In order to produce efficient medications and improve the pharmacological effectiveness of medications, delivery vehicles employ organic and inorganic based nanostructures such as application of a number of nanoforms, including liposomes, solid lipid nanoparticles, dendrimers, and solid metal-containing nanostructures as DDSs. By extending the drug half-life, making lipophilic pharmaceuticals more soluble, lowering the possibility of immunogenicity, and administering medications in a steady way, nano systems might improve medicinal efficacy. As a result, both the frequency of drug administration and its hazardous side effects can be decreased. furthermore, using improved penetration and persistence, nanoscale particles can aggregate passively in certain organs like cancers, Liu et al. (2009) and Orive et al. (2004). Targeting molecules involving nanomaterials guarantee the physically adherence of delivery system to sick tissue. A few nanomaterials discovered to carry medication across the blood brain barrier (BBB) to alleviate brain cancers when interacting with adequate targeting receptors and enhance the ability of immune system's diagnosis. The cells react by endocytosing the delivery system holding the active chemicals. The delivery system is combined with monitoring factors, such as fluorescent or radioactive materials then employed in imaging strategies to track the delivery of the drug to the target, Patra and Baek (2014) and Kabanov et al. (2002). The various physiochemical characteristics of nanomaterials are crucial for enhancing the effectiveness of medication delivery to certain sites. Metal nanoparticles (MNPs), Carbon nanotubes (CNTs), Fullerenes, Dendrimers, Graphene, Polymersomes, Nanocrystals, Liposomes, Polymeric NPs (PNPs), Quantum dots (QDs), proliposomes, microspheres, gels, prodrugs, and cyclodextrins are some of the more common varieties. MNPs for their wide surface area can

include a considerable medication dosage in drug delivery, also due to their small size, they can engage with the microorganism's cellular membrane, Tan et al. (2011). There are several uses for metal nanoparticles (NPs) coupled with antimicrobials in the food sector, water cleaning and therapeutic equipment and tools especially in biosensors. Additionally, they may form ligands with polymers to show anti-tumor, anti-cancer, and antibacterial properties, Lorenzo-Lamosa (1998).

Complex molecules known as carbon nanotubes (CNTs) are carbon-based tube-like objects formed from a recurrent sequence of sp^2-hybridized carbon atoms arranged in a hexagonal layout and wrapped into a cylinder ranging 2.5 to 100 nm. The quantity of carbon sheets rolled together determines whether a carbon nanotube has a single or multiple walls, and fullerene-like ellipsoid arrangements. Prior to being used as drug delivery vehicles, CNTs need to be functionalized by employing additional and oxidation processes. These materials are employed in medical settings. Drugs and biochemicals can be delivered to the mitochondria via fullerenes by passing them through the biological membranes, Saravana Kumar et al. (2012) and Sahil et al. (2011). Cells may readily absorb functionalized CNTs via passive and endosomal processes. Upon absorption, nanotubes align themselves perpendicular to the cell membrane before penetrating and diffusing through the lipid bilayer to reach the cytoplasm. The usage of magnetic CNTs, which spear a target cell by using an external rotating magnetic field, is one of the other cell permeation techniques being evaluated. The size, charge, and lipophilicity of the ligands on the CNTs' interface have a significant impact on the nanotubes' capacity to pass through cytoplasmic membrane. Additionally, patients receive CNTs using subcutaneous, abdominal, and intravenous methods, Sipai Altaf Bhai et al. (2012), Dutta et al. (2011) and Andrianov and Payne (1998). Smaller CNTs can penetrate the body more readily through oral methods after passing via intestinal columnar epithelium. CNTs have a tendency to stay in the injection site before gradually diffusing away from it and moving via the lymphatic system when administered subcutaneously. Targeting cancer cells that move in this way at metastatic stages may be possible with this. Injected CNTs intravenously spread rapidly to numerous interior organs, Genta et al. (2001).

Prior removal via the kidneys and liver, the tube's dimensions and its surface have a significant impact on its remaining time in the body. The functionalization with substances like polyethylene glycol can extend CNTs' residence time. Before using CNTs in therapeutic applications, extensive research must be done on their medicinal and hazardous profiles, Sree Giri Prasad et al. (2014). Dendrimers are a distinct family of nano polymers with hyper-branched, tree-like configurations that have the consistency, mono-dispersity of size, and surface functionalization capabilities make them desirable drug carrier vehicles (DCVs). Some usage of dendrimers including solubility, gene therapy, dendrimer-based drug delivery, immunoassay, and MRI contrast molecules are of great importance. They use nano-formulations for their utilization in medication administration. Pharmaceuticals are covalently bonded on dendrimers in the nano-construct technique, but in the formulation strategy, drugs are mechanically enclosed in a dendrimer utilizing non-covalent associations. Either complexation or encapsulation make it simple to incorporate medicinal ingredients. They can be changed to create sustainable molecules with significant bio-permeability and poor cytotoxicity, Vujačić Nikezić et al. (2020) and Abbasi et al. (2012).

Such networks help transfer therapeutic efficacy to the appropriate places. Drugs and other biologically active substances are mechanically incorporated into the space in dendrimers, or operate as DDSs due to a wide range of interactions, including their capacity to modulate for target-specific drug delivery, feasibility to improve with specified molecular mass, reasonable encapsulation performance, surface for functionalization, extremely low polydispersity index, and size, Cheng et al. (2008). The most common medicinal uses of graphene nanostructures at the moment are drug delivery. The promise of this nanostructured materials in the upcoming healthcare field was demonstrated by the quick rise of graphene-based medication delivery platforms. Their employment in clinical uses was made possible by their distinctive mono atomic planar configuration and related features, including a high surface area, chemical and mechanical stabilities, excellent electrical conductivity, and strong biocompatibility, Chung et al. (2010) and Dangi et al. (1998). Recently, rapid development of graphene-based nanotherapeutics in preclinical research indicates that these cutting-edge medicinal approaches may soon be used from the bench to the bedside. Since graphene has a large surface area, it is an allotropic form of carbon that enables medication delivery to tumor cells, but for its hazardous nature, it surfaces needs to be shielded from the direct contact, Dieckmann et al. (2003). In contrast to liposomes, polymersomes are much persistent vesicles made from amphiphilic polymers. However, these nanovesicles have many appealing qualities for in vitro/in vivo operations, they must be biocompatible and biodegradable in order to accelerate the translational potential and deliver formulations with medicinal value, Sagadevan and Periasamy (2014).

Polymersome nanostructures (PMNPs) are globular vesicular entities with fabricated amphiphilic building blocks including an aqueous suspension. Hydrophobic and hydrophilic subunits, such as poly lactic/glycolic acid and polyethylene glycol block polycaprolactone, make up the two parts of this unusual copolymer. Lately, polymeric vesicles for DDSs consisting of hydrophilic/hydrophobic di-block copolymers have been discovered. These structures also provide improved stability and flexibility, with liposomes adopting bilayer features such as biochemical makeup and density. Additionally, there are considerable differences in the interactions among lipids, proteins and polymeric bilayers, Zhao et al. (2016). Consequently, they have a significant impact on a DDSs's feature, such as in vivo blood flow time, where the blood flow duration of polymersomes in vivo improved as the density of the lipid bilayers did. Additionally, the characteristics of polymeric lipid bilayers are entirely distinct from single lipid bilayers and may be exploited to alter the carrier characteristics. Nanocrystals enable direct drug incorporation at the target region while reducing the buildup of carrier particles. With business potential in oral drug administration, nanocrystals become extremely stable in aqueous dispersions without stabilizers and then employed as a drug-delivery basis for severely water-soluble medications, Das et al. (2016).

As they may be readily absorbed by cancer cells, their promise for cancer therapy is crucial. The required dosage of medication administered into the cell should be nanoscale which act as its own carrier. Due to their nanoscale level, the nanoparticles are easily dissolvable in water. As a result, the particles are shrunk to the nano size scale which non-ionic surfactants and polymeric macromolecules stabilize their surface. As a result of the drug's expanded surface area and improved solubility disintegration, its plasma concentration increases due to its reduced dimension. There is rising attention in the creation and improvement of DDSs due to the intricacy of some illnesses and intrinsic cytotoxicity of some medications. A crucial technique for enhancing medication bioavailability or specialized distribution at the targeted site stands out as polymeric nanostructures. Polymers have the capacity to be the best choice for meeting the needs of each unique medication delivery system due to their flexibility. Covalent bonding among the drug and polymer carrier, hydrophobic interactions between the drug and carrier, and water-filled transport for hydrophilic drug inclusion are the methods they follow, Liu et al. (2011), How et al. (2013) and Ilbasmis-Tamer et al. (2016). By means of diffusion, desorption, and erosion, the NPs based medications are delivered into the desired position. Polymeric NPs can hydrolyze within the body to form biodegradable metabolite monomers and also carry medications to the site of action with limited harmful dosages. Therapeutics made from proteins and peptides can be coupled with polymers like polyethylene glycol (PEG) which these systems can prolong the half-life of medicines in plasma by preventing protein drug decomposition in the stomach and increasing hydrophilicity, Nguyen et al. (2017). These conjugated polymers do not recognize as foreign objects by white blood cells. These

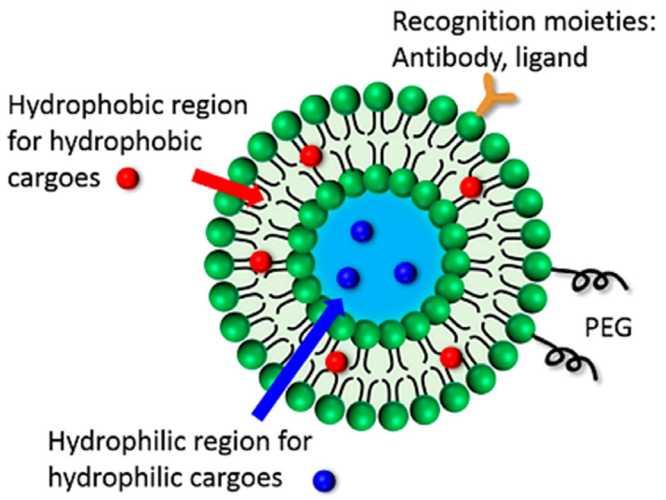

Fig. 1. Typical structure of liposomes. *Source:* Reproduced with permission from Ref. Cheng et al. (2022).

newly created polymer drug conjugates made through ring breaking metathesis copolymerization, could be quickly dissolved in aqueous solution, Rauta et al. (2016).

Drug aiming can be accomplished with the use of quantum dots (QDs) as nano-carriers for pharmaceuticals that increase the bioavailability of medications in biomedical domains. Additionally, a QD nano-carrier system for pharmaceuticals has the capability to provide targeted sickness location tracking, rapid identification and therapy. Additionally, QD nano-carrier systems for pharmaceuticals can boost targeted uptake, prolong in vivo circulating duration, optimize drug diffusion and metabolism in organizations, Whitesides (2003). In fact, quantum dots (QDs) are nanocrystals of semiconducting materials used for long-term monitoring of intracellular processes, in vitro bioimaging, and real-time detection. In terms of medical fields covered by its functionalities, QDs include the advancement of non-vectors for gene therapy, labeling of cells, screening and medicinal tools for the in vitro and in vivo tracking and assessment of biological molecules, immunoassays, DNA hybridization, monitoring systems, time-graded fluorescence imaging of tissues, transport vehicles for DNA, proteins, and drugs or cells, Xie et al. (2016).

3. Liposomes and their classifications

The lipophilic influence, which arranges amphiphilic molecules (phospholipids) to decrease thermodynamically unfavorable interactions between hydrophobic acyl-chains and neighboring aqueous environment, is primarily responsible for the rearrangement of phospholipids in aqueous solution, Fig. 1. The intermolecular attractions including Vander Waals, hydrogen bonds and electrostatic interactions help to mitigate this impact. A manufactured microscopic vesicle with an aqueous segment in the center and one or more concentric phospholipid layers around it is called a liposome which may include hydrophilic, hydrophobic, and amphiphilic materials, opening up a wide range of possible uses, Cheng et al. (2022).

According to their chemical matrix and method of intracellular distribution, liposomes may be divided into five categories including conventional, pH-sensitive, cationic, immunoliposomes, and long-circulating liposomes. However, the size of the vesicle is an important factor in regulating the circulation half-life of liposomes, and the number and size of the bilayers affect how much of the medication is encapsulated within the liposomes. Thus, liposomes were commonly categorized according to their size and number of bilayers into small unilamellar vesicles (SUV) with a size between 20 and 100 nm, large unilamellar vesicles (LUV) with a size more than 100 nm, giant unilamellar vesicles (GUV) with a size more than 1000 nm, oligolamellar vesicles (OLV) ranging 100–500 nm and multilamellar vesicles (MLV) with size less than 500 nm, Boman et al. (1994) and Chen et al. (2017a).

4. Importance of liposomal and nanoliposomal DDSs

Theoretically, drug delivery methods can make anticancer medicines more effective and less hazardous. With no exaggeration from tumor arteries, long-circulating macromolecular transporters like liposomes can take advantage of the increased permeability and persistence impact. Site-targeting controllable releasing, preservation of pharmaceuticals from destruction and elimination, improved medicinal value, and less harmful adverse consequences are just a few advantages of liposomes rather than ordinary DDSs. Liposomes are effective DDSs because they preserve the encapsulated materials from biological deterioration, increase the drug's half-life, regulate drug molecule delivery and also having good biological compatibility and security, Chen et al. (2016).

Additionally, liposomes have the ability to target their payload specifically to the problematic site via passive and dynamic methods, reducing systemic adverse effects, increasing the maximum allowed dosage, and enhancing treatment outcomes. Liposomal anthracyclines encompassing forms with significantly extended circulation such liposomal daunorubicin and pegylated liposomal doxorubicin with exceptionally effective drug encapsulation have caused to considerable antitumor efficacy with decreased toxicities. Either as a monotherapy and combination with other chemotherapeutic drugs, pegylated liposomal doxorubicin has demonstrated significant success in the management of breast tumor, Chernov et al. (2017). Thus, for the administration of various medications, further liposome constructions are being created. True molecular targeting will be a feature of the next delivery methods; immunoliposomes and other ligand-directed structures reflect the fusion of delivery methods and bio elements that can recognize tumors, de Smet et al. (2010). A few different sorts of liposomal medications are offered on the market despite the fact that liposomes serve as an ideal method for drug administration outside of the realm of specialized treatments. Liposomal drug delivery methods offering consistent formulation, better pharmacokinetics, and a level of passive or physiological targeting to malignant cells. Although, these transporters do not specifically target malignant cells, Allen et al. (1995). Compared to sensitive carriers like cationic liposomes, adjustments to liposome structure limit interactions with cancer cells as well as unfavorable interactions with plasma proteins and cell membranes. However, liposomes stay in the tumor stroma as a medication store after overdose introducing into the malignant cells. Enzymatic disintegration or phagocytic assault ultimately make liposomes vulnerable, releasing the medication for later distribution to cancer cells. Through partnerships with antibodies or other ligands, the next class of drug delivery carriers being developed for effective molecular targeting of tumor cells, Aisha et al. (2014).

Administering therapeutics or bioactive components to a particular location systematically while preventing exposure to non-target sites and increasing treatment efficacy is known as targeted drug delivery. In order to maximize the bioavailability and bio-distribution of the specified encapsulating location by conquering the barriers to cellular absorption, nanoliposomes are one of the most biocompatible nanocarriers utilized for targeted medication administration. In this approach, ligands and antigens are used to create the nanoliposome's membrane, whereas in prompted drug delivery, stimuli-sensitive production is used to induce the drug discharge, Dos Santos et al. (2005). The pathogenic components of the illness-related redox gradient, pH, tiny biomolecules, enzyme or hormone levels, glucose, or other systemic medication reactions are all included. Hyperthermia, ultrasound (US), light, and magnetic fields are only a few examples of environmental stimulation that are utilized to cause the delivery of drugs at the sick

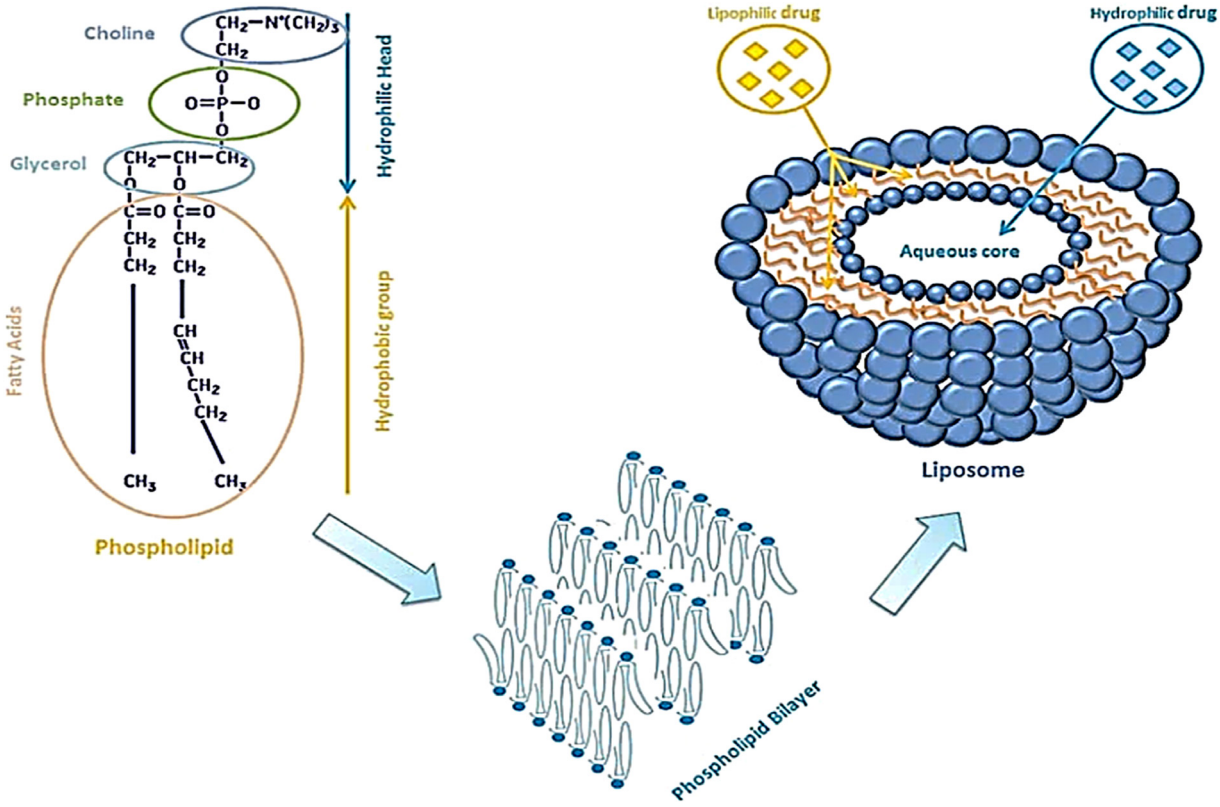

Fig. 2. A schematic participation of liposomes in DDSs. *Source:* Reproduced with permission from Ref. Laouini et al. (2012).

location. A clever DDS can go to the location where the medicine is supposed to distribute. Additionally, the substance may be released in reaction to particular external stimuli. They are now smart systems with the capacity for self-control, integrated sensing, tracking, and activation in response to signals and surroundings, Du et al. (2020) and Fan et al. (2016).

5. Factors affecting the nanoliposome performance

5.1. Permeability/Penetration capacity

The bilayer shape of nanoliposomes, allows for a significant amount of capacity to entrap hydrophobic and hydrophilic compounds functioning as leakage enhancer drawn a special consideration for drug delivery purposes, Fig. 2. In comparison to other nano DDSs, nanoliposomes' lipid bilayer may merge with other bilayers and because of its similarity to a cellular membrane, making it easier to penetrate the epidermal border and facilitating the delivery of the medicinal molecule's main components. For lower dimensions result in bigger surface areas and more responsiveness and regulation over the drug's release kinetics, size is a crucial parameter. Additionally, structure and shape are significant elements when creating effective nanoliposomes with high skin penetration and enhanced function. The nanoliposomes supplied with baicalein and functionalized to resemble skin components made from pseudo ceramides demonstrated their ability to efficiently transfer the poorly soluble medication while passing the epidermal resistance, Fan et al. (2014) and Flaten et al. (2013).

5.2. Drug loading capacity

According to the need to create dosage forms with the necessary payload and low drug degradation, the encapsulation performance and loading potential are critical factors for prospective uses of nanoliposomes. The initial drug/lipid mole proportion is the most important factor affecting the loading potential and treatment effectiveness of nanoliposomes. More specifically, when it is excessively significant (results beyond 0.95), poor loading potential is seen as a result of surplus medication that surpasses the liposomal loading potential. This overloading destroys the lipid barrier and results in a reduced final drug/lipid mole proportion. The creation of drug-loaded liposome formulations must consider a number of additional variables, including solubility, pH, drug characteristics, heat, and loading circumstances, Han et al. (2014).

5.3. Surface modification

The clinical relevance of a therapeutic agent relies on its accessibility at the intended location and its special quantity during a determinate time. In addition, limiting medication access to non-target regions is crucial to prevent probable adverse consequences. By altering the pharmacokinetic aspects of the drug, such as its dispersion, uptake, and excretion, nano DDS, such as nanoliposomes, have contributed to an improvement in therapeutic effectiveness and security, Hızır-Kadı et al. (2020). Surface treatment of nanomaterials caused to prevent nanoparticles from being phagocytosed and eliminate from the blood vascular system following intravenous administrations. Moreover, this type of modification on nano-surface based DDSs can overcome the problem of phagocytic clearance of nanostructures. Nanoliposomes are more suited for cellular uptake since they resemble biological barriers. Typical nanoliposomes can have their surfaces modified to increase durability while maintenance, promote phospholipid bilayer penetration, and keep the deposited medicine, Guo et al. (2011).

5.4. Stability/Shelf life

In nanoliposome based DDSs, nanoliposome persistence is a crucial factor. Beyond particle diameter, the potential treatment effects of

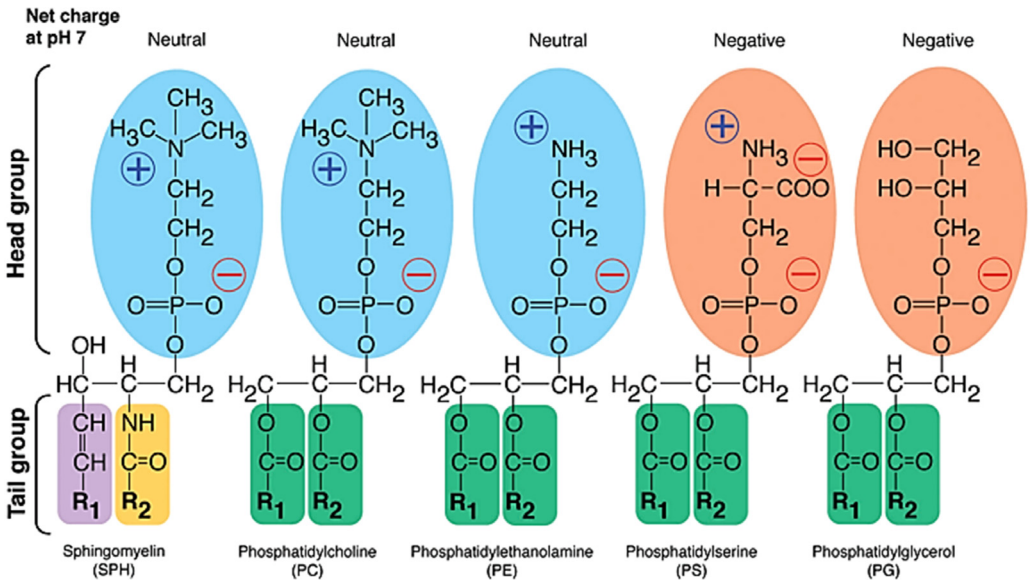

Fig. 3. Commonly phospholipids for the synthesis of liposomes;.
Source: Reproduced with permission from Ref. Kraft et al. (2014).

nano-liposomal-encapsulated medicines depending upon their stability-related lifespan and dispersion inside the body. The consistency of the manufactured components and the presence of stabilizers throughout maintenance or application are key factors in the preservation of dimensionality. In order to maintain their dimensions at a nanoscale level, nanoliposomes should involve a sufficient consistency pattern. Nanoliposomes can often be diluted in aqueous media without affecting the dispersion of their vesicle sizes since they are metastable. To reduce the aggregation in anatomical structures, biological substances need to be properly removed from the organism, Huang et al. (2016) and Isacchi et al. (2011). Because of this, nanoliposomes must be moderately stable in order to be more biodegradable and clearable, which leads to lesser bioaccumulation and positive risk-benefit ratios. Nanoliposomes' active surface may interact with bioactive compounds or living cells to start complex processes that lead to agglomeration, solubility, destruction, accumulation and deposition, Isacchi et al. (2012).

6. Synthesis of nanoliposomes

In contrast to surfactants, liposomes lack thermodynamically persistent nanostructures and do not form naturally in a water media. Energy is required for the creation of liposomes, and the quantity of energy input might vary greatly based on the kind of liposome. When the polar lipids that make up the bilayer are evenly distributed in an aqueous solution while being gently stirred, MLVs are readily produced. However, to disassemble the MLV and MVV formations and make vesicles with the monomodal pattern, LUVs and SUVs need to be produced, Angst and Drover (2006). Due to the fact that liposomes and emulsions are temporarily stable, numerous emulsion methods are employed to create liposomes, Fig. 3. So, when phospholipids, such as lecithin, are trapped in water to create one or more bilayers, lipid vesicles are created. When enough energy is present, molecules are used to segregate them. As energy enters, lipid molecules organize into bilayer vesicles in order to reach dynamical balance in the aqueous medium, Ramishetti and Huang (2012). The kind of employed lipids and also the presence of sterols are crucial factors in defining the membrane's curvature. Phospholipids that form bilayer lamellar formations, like phosphatidylcholine, can bend and create vesicles. Despite this, in the absence of stabilizing substances like sterols, these formations are not particularly stable due to structural restrictions, Cullis and de Kruijff (1979).

The best strategy for creating liposomes and nanoliposomes depends on a number of variables, such as the physicochemical features of trapped materials, the liposomal constituents, the atmosphere that is distributed on the lipid vesicles, the material's hazardous impacts and efficient concentration, extra procedures entailed in vesicle transfer and ideal size. Manufacturing related organic solution including phospholipids, cholesterol and hydrophobic chemicals is often the first stage in creating conventional liposomes. Secondly, the solution is evaporated to create a thin film. The addition of the aqueous medium and the hydrophilic material, accompanied with the application of the proper heat and potential power, causes a sheet of hydrophobic moieties to develop, which then separates from the aggregate to produce MLVs, Edidin (2003). MLVs can exhibit best conservation of the reactive chemicals because of the number of lamellas that the substance must travel in order to access the exterior of the vesicle. This is because the water-soluble constituents of liposomes are often released by their permeability through the membrane. The primary issues with MLVs are their ineffectiveness in capturing them and the limited amount of water that is trapped. As a result, several methods have been employed to encapsulate a greater quantity of the potent substance, Table 1. By enhancing the amount of the water phase captured in the vesicles and using high lipid quantities, it is possible to boost the effective entrapment. The produced vesicles are of varying sizes and have a range of characteristics for use with diverse techniques. Due to their enormous diameter, size variability, instability, and heterogeneity amongst preparations, MLVs have a restricted usage in practical uses. Producing a single-lamellar vesicles that are smaller and better able to encapsulate hydrophilic chemicals is possible by being composed of bilayers of phospholipid moieties around an internal aqueous nucleus, Allen et al. (1991) and Lee and Low (1995). Phosphatidylethanolamine, phosphatidylglycerol, phosphatidylcholine, phosphatidylserine, and phosphatidylinositol are the main building elements of the liposomes. Phosphatidylcholine (lecithin) and phosphatidylethanolamine comprise most liposome compositions. Water, hydrophilic polymer conjugated lipids, cholesterol and other substances are possible components of liposome bilayers, Kraft et al. (2014).

One of the crucial elements should be evaluated is the process of liposome synthesis and the key steps in their development, encompassing their physicochemical features. A key aspect in the formation of liposomes is their chemical composition. In actuality, the primary chemical constituents of liposomes are lipid and phospholipid units and

Table 1
Different liposomal structures and their synthesis methods.

Entry	Liposomal structures[a]	Liposomal synthesis method[a]	Size (nm)	Ref.
1	Au in lipid NSs	RM	53 nm	Bromma et al. (2019)
2	PTX@GNPs in liposomes NSs	TFH	3.41 nm (Au core)	Bao et al. (2014)
3	Liposomal ibuprofen NSs	LFH	<6 μm	Mohammed et al. (2004)
4	Liposomal Acetazolamide NSs	RFE	<7.6 μm	Hathout et al. (2007)
5	Liposomal salidroside NSs	EI	<100 nm	Fan et al. (2007)
6	Liposomal BSA NSs	EDEm.	<30 μm	Dai et al. (2006)
7	Au in liposome NSs	TFH	105 nm	Chithrani et al. (2010)
8	Au@PFH NCs in lipid shell NSs	TFH&DE	108 nm	Liu et al. (2017)
9	GNS@CTS@RES-lips/Au NSs	Mediation of CTS	115 nm	Wang et al. (2017)
10	Au@Ag@MMTAA in DSPE-PEG2000-NH2 liposomes NSs	TFH	215 nm	Zhu et al. (2018)
11	Liposomal cyclodextrin form of Metronidazole and verapamil-HCl NSs	Spray drying	<395 nm	Skalko-Basnet et al. (2000)
12	Liposomal Au NSs	TFH	<150 nm	Rengan et al. (2014)
13	Cluster liposomal Au NSs	TFD	<150 nm	Zhang et al. (2016)
14	Liposomal (SiO_2@SP-Fe_3O_4) NSs	LFH	53 nm	Sharifabad et al. (2016)
15	Liposomal E. coli plasmid DNA NSs	Heating	<2 μm	Moazam Mortazavia et al. (2007)
16	Liposomal ketoprofen/ciprofloxacin lactate and propranolol-HCl NSs	Freez drying	<410 nm	Li and Deng (2004)
17	Liposomal (PTX/SP-Fe_3O_4) NSs	TFH	3.41 nm (Au core)	Zheng et al. (2018)
18	Liposomal (MNPs in MFLs) NSs	Extrusion	NPs:13 nm MFL: <150 nm	Aranda-Lara et al. (2020)
19	Liposomal Calcein NSs	Freez drying	100 nm	Cui et al. (2006)
21	gonadore line- functionalized Mit- loaded MLs (Mit-GML) NSs	LFH	Mit-GML: <150 nm	Mitchell et al. (2013)
22	(SP-Fe_3O_4 NPs@PGN-L-IO/DiR) NSs	LFH	PGN/L/IO/DiR: <115 nm	Musielak et al. (2019)
23	Liposomal Glucose NSs	Supercritical RFE	<2 μm	Imura et al. (2002)
24	Liposomal E. coli rh- Cu/Zn-SOD NSs	–		Wagner et al. (2002c)
25	Liposomal SP-Fe3O4@silica NSs	TFH	Hybrid size: 150 nm	Zhang et al. (2014)
26	PEG@liposomal doxorubicin NSs-Cu-64[a]	No information	NR[a]	Patil-Sen et al. (2020)
27	dual gadolinium liposomal contrast agent (DM-Dual-Gd-ICG)	LFH	>150 nm	Bray et al. (2018)
28	Liposomal IMC@BDP NSs	Membrane contactore	<180 nm	Jaafar-Maalej et al. (2011)
30	SP-Fe_3O_4@Liposome@ICG and RGD NSs	TFH&Extrusion	>150 nm	Ravoori et al. (2016)
31	Liposomal MM-DX-929-Cu-64[a]	Merrimack Pharmace uticals	104 nm	Lorente et al. (2018)
32	Liposomal CA4P-UML NSs	RFE	209 nm	Thébault et al. (2019)

[a]PTX: Paclitaxel; PEG: Polyethylene glycol; PTT: Photothermal therapy; DSPE: 1,2-Distearoyl-sn-glycero-3-phosphorylethanolamine; MMTAA: 2-mercapto-4-methyl-5- thiazole acetic acid; CT: Computed tomography; ICD: Indocyanine green, RGD: Arginine-Glycine-Aspartic peptide; CA4P: Combretastatin A4; DiR: Near-infrared dye; MM-DX-929-64Cu-liposomal doxorubicin PET Agent (Merrimack Pharmaceuticals, Inc. Cambridge, MA, USA); UML: Ultra magnetic liposomes; NR: No report; NSs: Nanostructures; GNPs: Gold nanoparticles; SP: Supermagnetic Iron oxide; RM: rapid-mixing; TFH: Thin film hydration; LH: Lipid hydration; RFE: Reverse-phase evaporation; EI: Ethanol injection; EDEm.: Emulsion double emulsification; DE: Double emulsion; CTS: Chitosan; TFD: Thin film dispersion; LH: Lipid hydration; LFH: Lipid film hydration.

also the sterol that is used frequently in the formation of lipid vesicles is cholesterol, Lee and Low (1994).

Cholesterol is primarily used in liposome formations because it increases the consistency of the vesicles by modifying the fluidity of the lipid bilayer, preventing the crystallization of the acyl chains of phospholipids, generating steric hindrance to their motion, making the liposome more durable, and reducing the permeability of the lipid membrane to solutes. The crucial physicochemical characteristics of liposomes include variables like phase transition temperature, ionic strength and pH. Such nanomaterials typically have limited permeability to the substances that they are encapsulating, but at elevated heat, their permeability may vary. Phospholipids have a significant impact in the thermal properties of liposomes and can undergo a phase transition (Tc) at temperatures below their final melting point (Tm), Plank et al. (1996) and He et al. (2010). According to the amphiphilic nature of phospholipids, when present in an aqueous system, hydrophilic head groups remain in touch with water molecules whereas hydrophobic head entities are shielded from the aqueous phase by accumulating associations formed by phospholipids. If enough energy is available, phospholipids can self-assemble into organized, closed bilayer nanoliposomes or liposomes; it is crucial to note, however, that this mechanism is not dynamic. By dissolving these molecules together with the lipids, specific vitamins, medications, nutrients, and other lipophilic compounds can also be captured in liposomal bilayers. The following sections provide clarification on a few of the methods that are often used for liposome production, Chonn et al. (1991). There are various traditional ways to make liposomes. The manner that lipids are removed from organic solvents and subsequently re-dispersed in water medium differs across the different techniques. These actions are carried out singly or frequently in combination.

6.1. Thin-Film Hydration-Sonication (TFHS) method

In the TFHS approach, phospholipids are mixed with lipophilic medicines and dispersed in a polar solvent. The solvent is then expelled above the phospholipid transition point. Evaporation of remaining organic solvents before water intake and under a vacuum desiccator for 24 h or more caused to formation a film at the bottom of the flask. In the presence of distilled water or a buffer solution, the hydration is performed while being stirred. To minimize vesicle size and homogenize the material, the sample is then sonicated for 1 h, Chen et al. (2017b).

6.2. Ethanol Injection (EI) method

In the EI approach, an ethanol solution of phospholipids is administered into a water phase under controlled situations, vigorous agitation, and injection heat above the lipid transition point. Following that, the solution is mechanically stirred on a magnetic stirrer and evaporated at ambient temperature to eliminate any remaining solvent, Chen et al. (2012).

6.3. Reverse Phase Evaporation (RPE) method

Using an ultrasonication, the lipid mixtures are solubilized in RPE after being dispersed in an organic solvent. The combination is then mixed with a liquid solvent containing stabilizers. A rotary evaporator is then used to remove the solvent in order to encourage the production of a thick film and then for removing the rest of organic solvent, further liquid solution is applied. To homogenize the particle magnitude, the

final mixture is subjected to centrifugation, sonication, or dialysis. In order to clean the system and prevent the lipid blends from degrading, nitrogen atmospheres might be used, Chen et al. (2015).

6.4. Detergent dialysis

When lipids are dissolved in detergent, specified mixed micelles ranging 40 to 180 nm are produced. Phospholipids create homogeneous unilamellar vesicles with a reasonably considerable enclosed volume as the detergent are subsequently eliminated by managed dialysis. For the creation of liposomes, other approaches including calcium-induced fusion, nanoprecipitation, and emulsion procedures have already been applied. Despite the toxicity of organic solvents for ecosystem and public health, the vast volumes of organic solvent required by these conventional ways, however, must be completely removed. Additionally, the requirement of typical procedures for a lot of energy and several stages for size homogeneity is caused that they are inappropriate for producing liposomes in significant quantities. Therefore, a variety of widely popular procedures were considered as large-scale liposome production processes, including the Heating Method, Spray Drying, Freeze Drying, Super Critical Reverse Phase Evaporation, and other altered ethanol injection approaches, Singh et al. (2017) and Balla et al. (1990).

6.5. Supercritical Fluid (SF) method

The technique was created to minimize the danger and usage of organic solvents for synthesizing nanoliposomes. Fast growth of supercritical solutions and supercritical antisolvent (SAS) are the two most popular methods used to create nanoliposomes using a phospholipid-containing organic solvent as a co-solvent. Using the supercritical fluid as an anti-solvent should be mixable to concentrate and deposit the lipid component in the creation of nanostructures. In the RESS technique, solutes are mixed in the supercritical fluid at high pressure, after depressurizing the solution which finally deposited by fast growth in order to facilitate rapid condensation. Following sufficient particle production, supercritical CO2 serves as a solvent in this instance, Yu et al. (2017).

6.6. Spray-drying

The straight spray-drying of a lipid and drug combination was used in the creation of liposomes since spray-drying is an extremely straightforward and manufactured relevant process. Spray-drying is thought to be a quick, one-step technique used in the creation of nanomaterials which lecithin and mannitol are suspended in chloroform to create liposomes. The composition was spray-dried after being sonicated for some minutes. The dry sample was stirred while being hydrated with various quantities of phosphate buffered saline (PBS; pH 7.4). The amount of water phase utilized to hydrate the spray-dried component had a major impact on the liposomal size. However, mannitol is crucial in expanding the lipid mixture's surface area, which makes it possible for the spray-dried material to be successfully hydrated, Ahmed et al. (2018) and Li et al. (2012).

6.7. Freeze drying

The foundation of this novel approach is the production of a homogeneous lipid dispersion in water-soluble carrier substances. In the right proportions, water-soluble carrier molecules like sucrose and lipids that form liposomes were dissolved in tert-butyl alcohol/water co-solvent mixtures to produce a transparent, isotropic monophase solution. The monophase solution was then filtered for sterility and put into vials for freeze-drying. The lyophilized substance naturally generates a homogeneous liposome mixture when water is added. The lipid/carrier ratio is the main factor impacting the size and the polydispersity of the liposome formation therefore, the TBA/water cosolvent system was employed, Zhang et al. (2008).

6.8. Micro fluidization

The liposomes were produced utilizing a microfluidic hydrodynamic concentrating (MHF) device by infusing the lipid and water phases into a microchannel. Because of the narrow channel sizes and relatively modest flow rates, microfluidic flow is often laminar. When numerous flow streams are injected in a microchannel, well-defined mixing is then achieved by interfacial diffusion. Controlling the flow velocity was the key factor in regulating the liposomes' size, Gibis et al. (2014).

6.9. Membrane contactor

Membrane contactor is used in conjunction with the ethanol injection approach to produce liposomes on a massive scale. This technique involved pressing a lipid phase (ethanol, phospholipid, and cholesterol) through a membrane with a predetermined pore size. The organic phase could flow through the membrane using nitrogen gas at pressures lower than 5 bar. During the same period, the produced liposomes within the membrane device were swept away by the aqueous medium as it flew tangentially to the membrane surface. The benefits of the novel method include its straightforward architecture, ability to scale up, and control over liposome size through operational factor modification. The usual batch method is thus replaced with prospective large-scale constant operations using these approaches, Chatterjee and Bhattacharjee (2013).

6.10. Supercritical Assisted Liposome formation (SAL)

The SAL involves a dense gas, like carbon dioxide (CO_2), to improve the blending of the organic phase (phospholipids and ethanol) with water and to eliminate any remaining ethanol from the suspension of liposomes. for creation a gas-expanded solution, the organic composition is pushed into a static mixer with CO_2 at a specified heat and pressure, typically 100 bar and 40 °C. The resultant ethanol expanded solution is injected into a high-pressure chamber together with an aqueous phase. The aq. phase is instantaneously poured all over a nozzle. Lastly, ethanol is collected in a separator by CO_2 flushing out from the chamber under pressure and at ambient heat, separating it from vesicles and aqueous dispersion. The viability of this method for producing nanoliposomes provides for good management over particle diameter and dispersion as well as great trapping effectiveness, Frenzel and Stefen-Heins (2015).

6.11. Expanded Liquid Organic Solution Depressurization (ELOSD)

A mixture comprising lipids and an organic solvent is added to a vessel at operating temperatures (O.T) and atmospheric conditions (Atm. P) to execute this procedure. The lipid is then expanded by introducing a significant volume of CO2 to create an expanded solution. In fact, the lipids must be dissolved in the CO2-expanded solvent to develop of a single phase within the high-pressure chamber until it reaches the operating pressure (O. P). Furthermore, to improve the homogeneity of the vesicles, depressurization of CO2-the expanded solution is carried out over a stream of water media from (O. P) to (Atm. P) including a surfactant. The CO2-expanded solution is pushed down in this last stage while maintaining a consistent internal pressure using a stream of N2 at O. P, Sebaaly et al. (2015).

6.12. Gas Saturated Solution Particles (GSSP)

The PGSS, for the purpose of encapsulate therapeutic substances in liposomes, includes saturating a solute with CO2 at elevated pressure in an emulsification vessel, expanding the gas-saturated platform, and inducing particle production by hardening the mixture as soon as the heat rapidly drops, Li et al. (2011).

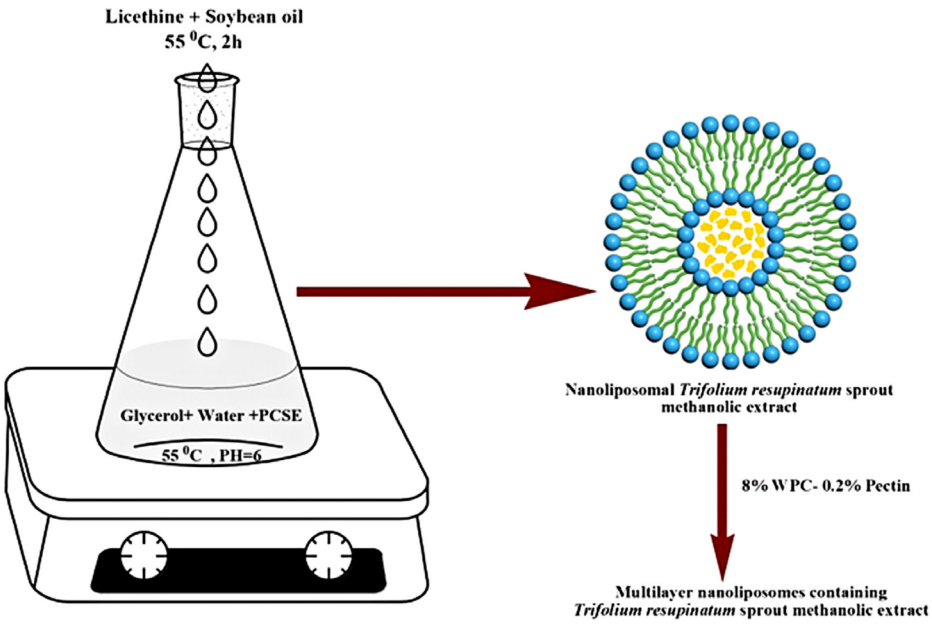

Fig. 4. Persian clover sprouts for the synthesis of nanoliposomes. *Source:* Reproduced with permission from Ref. Zahra Sayyed-Alangi and Nematzadeh (2019).

6.13. Depressurization of an Expanded Solution into Aqueous Media (DESAM)

At mild atmospheric conditions under 60 bars, a combination of lipids in an organic solvent is pumped into an expansion chamber in the DESAM. The combination was then pressurized by the dense gas, which also heated it into an aqueous medium. The organic solvent is removed from the process when dense gas is supplied to sustain pressure. With the gas exiting the system, the remaining solvent will be kept to a minimum and may be recovered and recycled, Joyce et al. (2017).

6.14. Heating method

It is a technique for producing nanoliposomes quickly without the use of dangerous chemicals. The phospholipids and inactive ingredients are soaked in an aqueous solution for 1–2 h under inert environment. To achieve optimal component diffusion in the water phase, the components are mechanically stirred following the inclusion of a polyol that serves as a co-solvent or dispersant at a heat up to 120 °C for 30 min. Based on how sensitive they are to heating, medicinal components can be introduced at either a high or mild temperature once the components have been evenly distributed, Wang et al. (2013).

6.15. Mozaffari method

Through this technique, nanoliposomes may be created in a single operation without the requirement for solvents, detergents, or prehydration. A warmed combination containing the therapeutic substance is supposed to encapsulate and a polyol is introduced before the liposomal components. The solution is then warmed while being stirred in a nitrogen environment. If cholesterol is to be included in the formulation, it must be introduced in the water phase and stirred at high degrees in a nitrogen environment prior to the other phospholipid ingredients are combined. The nanoliposome suspension is then heated beyond the lipid transition point in an inert environment to provide sample annealing and stabilization, Li et al. (2013). In order to create the diverse nanoliposomes, Alangi et al. researched the Persian clover sprout (PCSE). They used a number of combinations with varied proportions of soybean oil, lecithin, and the extract, Fig. 4. The composition that contained 30% oil, 5% lecithin, and 2% extract produced the most durable nanoliposomes examined utilizing zeta potential and size assessment methods. The measurements of the nanoliposomes' sizes revealed that their z-mean size varying from 282.5 to 491.2 nm. After that, whey protein and pectin were used to biofunctionalize the nanoliposomes. Then, they introduced obtained nanoliposomes to soybean oil to test their impact in preventing oxidation, Zahra Sayyed-Alangi and Nematzadeh (2019).

According to Hasan et al. Loureirin B (LB) Loaded Nanoliposomes were created using a thin-film approach to regulate drug distribution, hydrophobicity, and efficacy for a variety of biological purposes. Thin-film evaporation was used to create the phospholipid and cholesterol-based nanoliposomes (NLs) as a drug transporter for LB. The dimension of the NLs' molecules (58 to 94 nm) was substantially correlated with their lipid content. The LB-loaded NLs also demonstrated a high-potential of 51.2 mV supporting their good stability, improved distribution in chosen solvents/cell plasma, and homogeneous drug administration, Fig. 5. The highest dosage of the LB-loaded NLs composition, the removal rate half-life, the area under the curve, and plasma clearance all improved as a result of the LB-loaded NLs' in vivo testing, Hasan et al. (2019).

Espinoza et al. developed an improved reverse phase evaporation technique for making nanoliposomes, Fig. 6. The ecofriendly Ag NPs had a good encapsulation rate and more stability when they were placed in liposomes with cholesterol. Particle size, polydispersity index, zeta potential, and scanning electron microscopy were used to examine the liposomes loaded with Ag NPs. The findings revealed that Ag NPs inserted into liposomes had a homogeneous range of sizes of 321 to 373 nm, a zeta potential about −40 mV, and a polydispersity index of 0.2, Espinoza et al. (2020).

Lujan et al. investigated the creation of nanosized liposomes for the delivery of microRNA to breast tumor cells utilizing the ethanol injection technique. In their experiment, chemicals were diluted with PBS, ethanol-dissolved and incubated with RNA. The resulting liposomes receive one day of dialysis after continuous agitation. The samples are kept at 4 °C (with or without sonication). The fact that manufactured liposomes have multi-model size populations is shown by both samples (A and B). The created liposomes were frozen at 80 °C for four hours, Fig. 7. The frozen particles were then lyophilized overnight (between −100 and −120 degrees Celsius) to create a powder. PBS

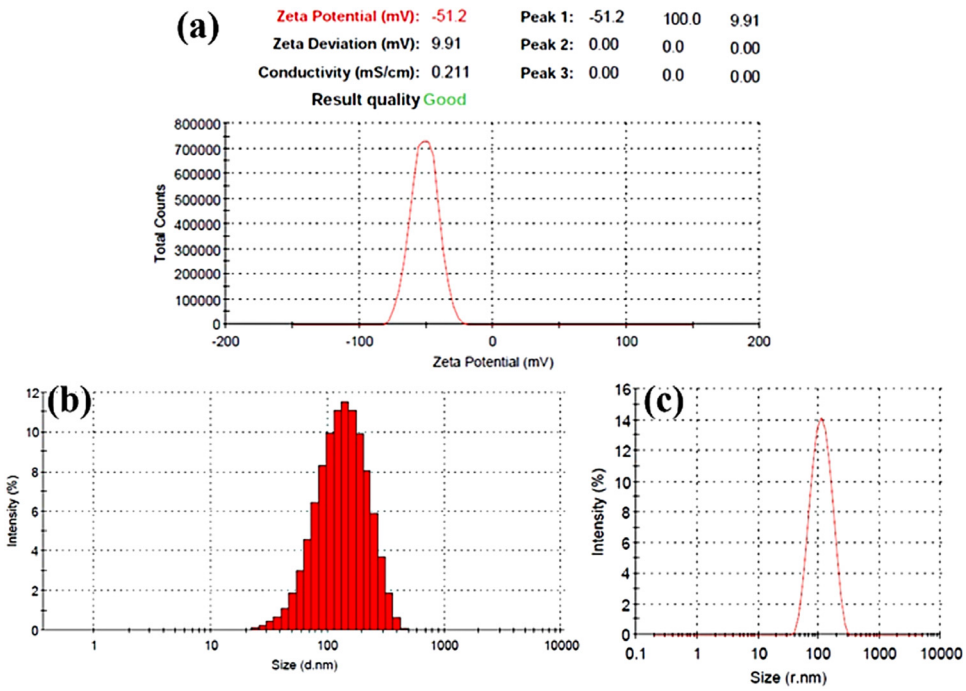

Fig. 5. (a) ζ-Potential of LB-loaded NLs; (b, c) size distribution of LB-loaded NLs.
Source: Reproduced with permission from Ref. Hasan et al. (2019).

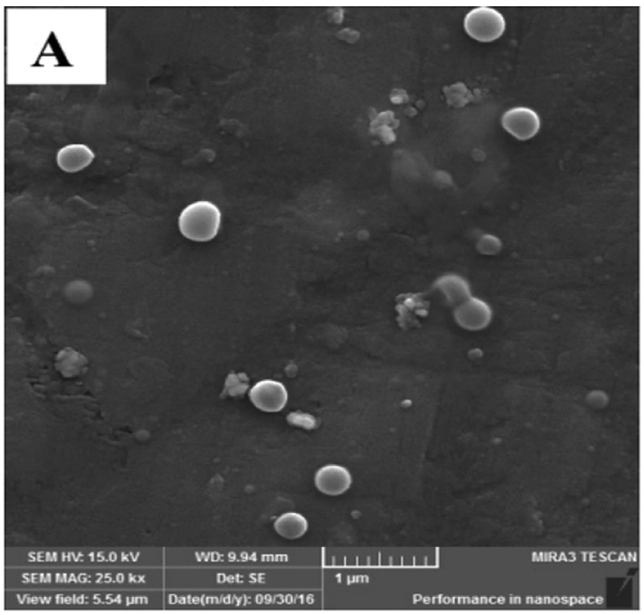

Fig. 6. The SEM of LAg NPs prepared by modified reverse phase evaporation method.
Source: Reproduced with permission from Ref. Espinoza et al. (2020).

was used to obtain restoration at the initial liposome formation dosage. The microRNA-loaded nanoliposomes have been kept for months in a dry state and continue to sustain encapsulation even after prolonged storage times, Lujan et al. (2019).

Following the thin film hydration approach, Othman et al. reported creating liposomes by using a variety of surface changes. The 1,2-dimyristoyl-sn-glycero-3-phosphocholine (DMPC), poly (diallyl dimethyl ammonium) chloride (PDAA) polymer, and silica nanoparticles were used to create three distinct liposome-based nanocapsules. In order to thoroughly encapsulate curcumin within the liposome, PDDA and silica nanostructures were deposited on the surface of the liposomes using a layer-by-layer construction process in which encapsulating curcumin into the core of the functionalized liposomes increased the antitumor effect of curcumin, Fig. 8. The produced nanocapsules were characterized using zeta potential, TGA, DLS, XRD, SEM, and fluorescence spectroscopy. The outcomes demonstrated that as the number of layers at the liposomes' surface rose, the discharge of curcumin from the nanocapsules reduced, Othman et al. (2022).

Fabrication of Mannosylated neoglycolipids for liposomal delivery usages was reported by Mousavifar et al. They focused on a self-contingent method to make neoglycolipids having two lipid tails with different alkyl chains, an aromatic scaffold, and one exposed mannose residue, Fig. 9. Utilizing novel one-pot improved synthesis technique, the carboxylic acid- and azido-ending lipid tails were ligated. Dynamic light scattering (DLS) studies and TEM were used to establish the creation of persistent neoglycoliposomes of controlled and optimal sizes (100–400 nm), Mousavifar et al. (2022).

According to Salem et al. the thin film hydration approach was used to create nanoliposomes of the osteoporosis medication alendronate sodium (ALDS) utilizing phosphatidylcholine/cholesterol and various concentrations of starch. The vesicles were covered with more starch as a result of the entrapment of the ALDS/starch combination, which improved encapsulation performance and in-vitro persistence, Fig. 10. The range of liposome particle sizes increased with rising starch content as varied from 94 nm to 298 nm. In addition to the liposomes' spherical form confirmed by TEM, the zeta potential data revealed that the liposomes exhibited high zeta values after being covered with starch treatments (0.1–0.5% w/v) ranged from −12 mV to −39 mV. Additionally, a recent investigation on the impact of starch level on the liposome encapsulation performance of ALDS found that raising the starch level boosted ALDS's proportion encapsulation capacity, Salem et al. (2018).

Huang et al. combined two techniques to create nanoliposomes using microfluidic devices, namely micro-dispensers and a sonicator. The liposomes' size was dramatically lowered by sonication. As the proportion of the buffer to solvent flow rate rose, the particle size dropped, Fig. 11. The resultant finest nanoliposomes particle sizes were attained at a volumetric flow rate of lipids of 0.374 ml/min. Ultrasound and microfluidic technology combine together to create

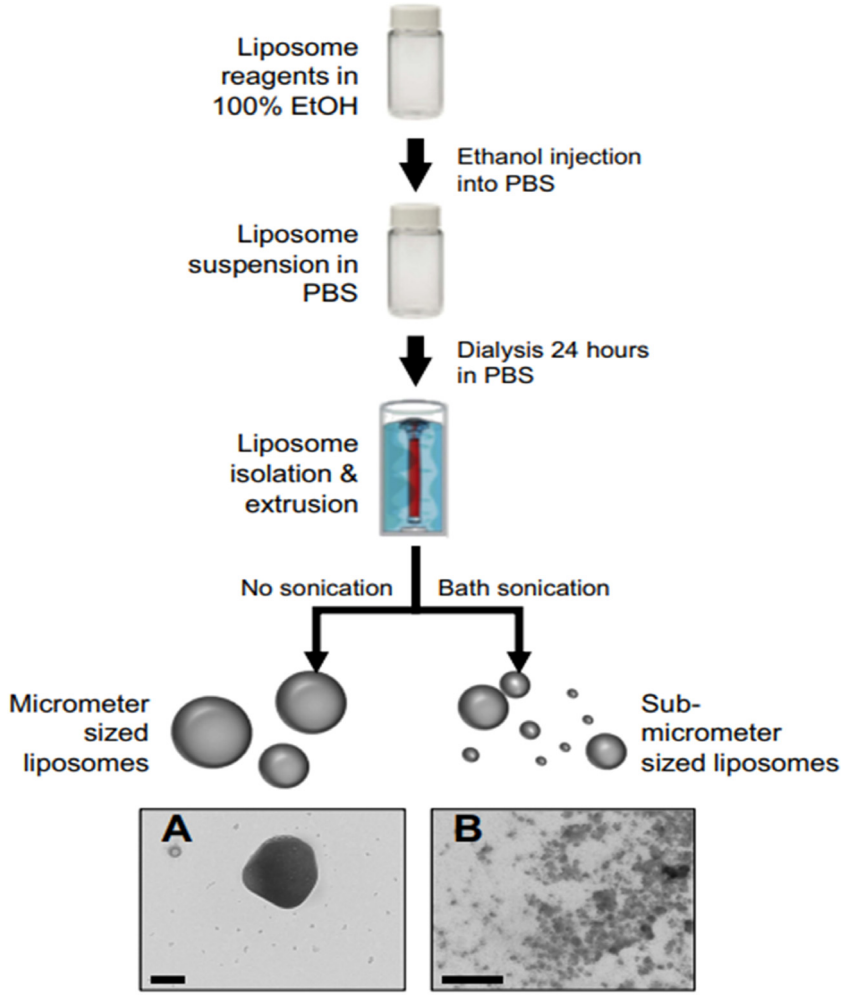

Fig. 7. Synthesis scheme of the nanoliposomes preparations. *Source:* Reproduced with permission from Ref. Lujan et al. (2019).

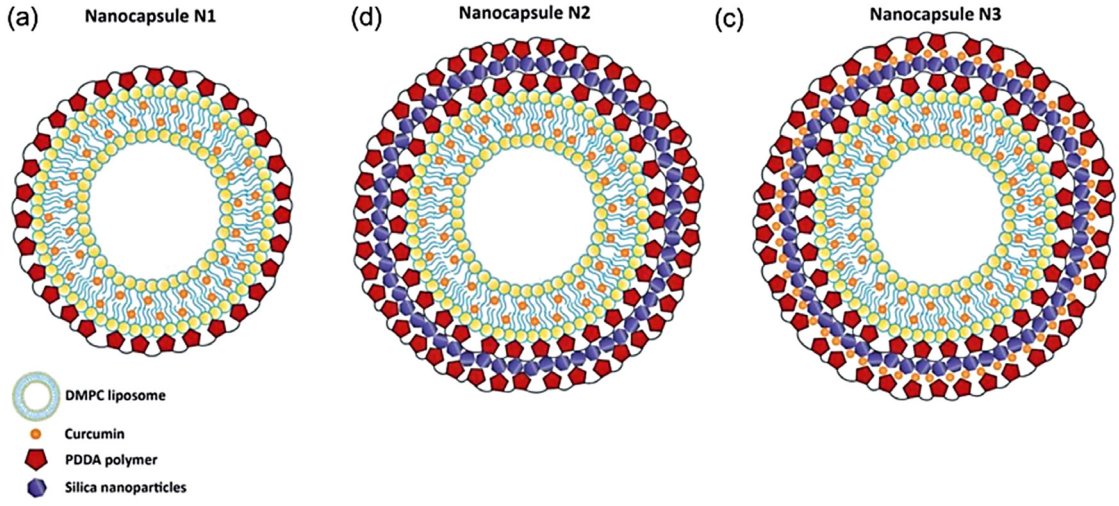

Fig. 8. An illustration of liposome based nanocapsules,. *Source:* Reproduced with permission from Ref. Othman et al. (2022).

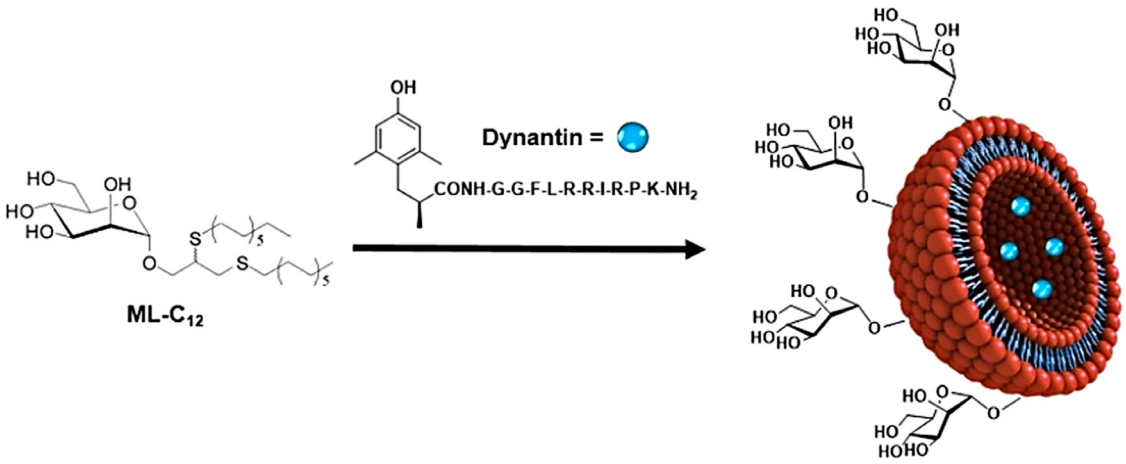

Fig. 9. Synthesis of Mannosylated liposomes C12-alkyl mannopyranoside (ML-C12).
Source: Reproduced with permission from Ref. Mousavifar et al. (2022).

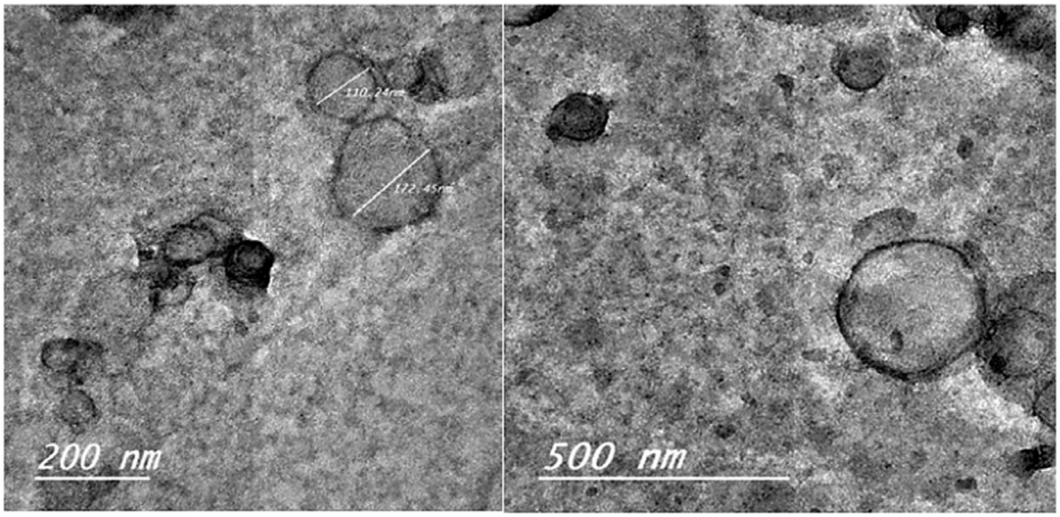

Fig. 10. TEM images showing ALDS liposomes.
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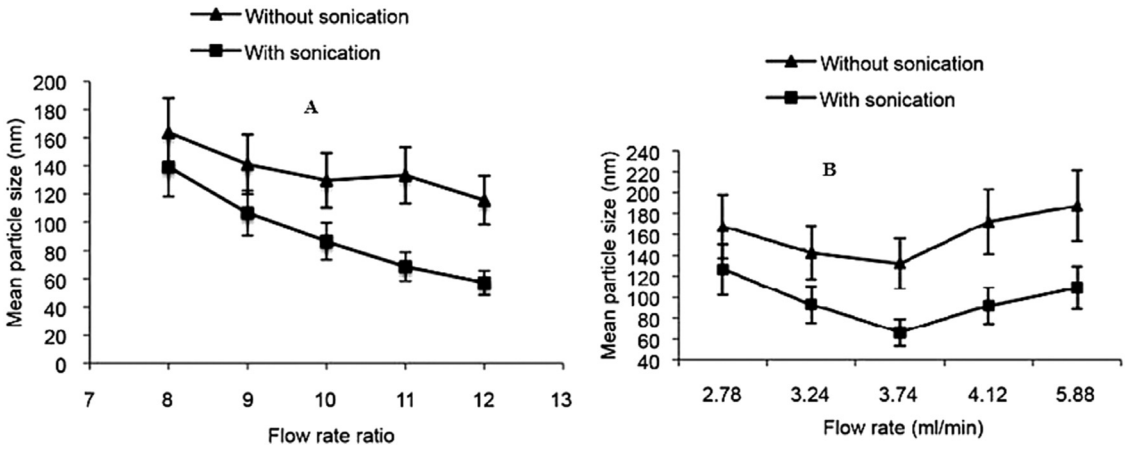

Fig. 11. (A) Flow rate ratio versus particle size of liposomes synthesized in microfluidics with or without sonication. (B) Flow rates versus particle size of liposomes prepared in microfluidics with or without sonication.
Source: Reproduced with permission from Ref. Huang et al. (2010).

liposomal nanostructures with a restricted size dispersion, Huang et al. (2010).

The preparation of palmitoyl oleoyl phosphocholine (POPC) liposomes were reported by Gudlur et al. using a thin film hydration

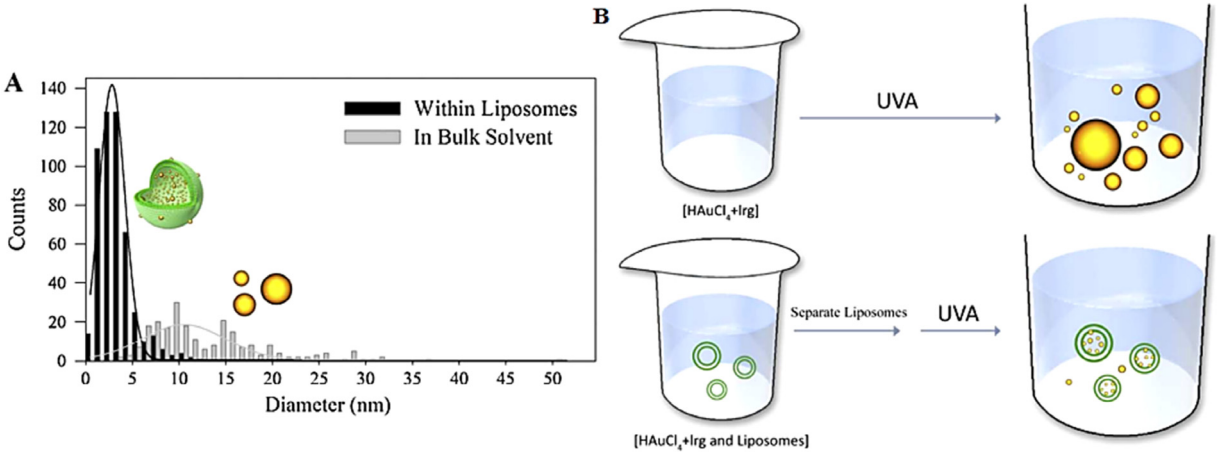

Fig. 12. (A) Size distribution study of Au NPs in bulk solvent and encapsulated in POPC liposomes. (B) the photochemical synthesis of AuNPs in bulk solvent (top panel) and within liposomes (bottom panel).
Source: Reproduced with permission from Ref. Gudlur et al. (2015).

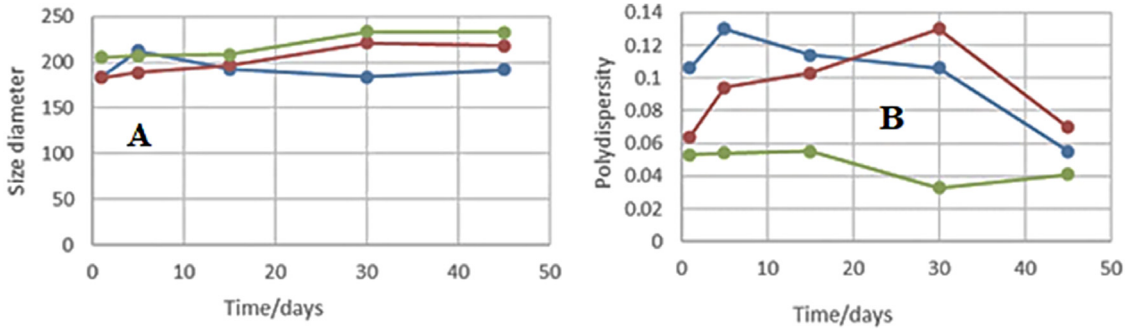

Fig. 13. (A) Size diameter of Liposomes as a function of time, (B) Recording of liposomes polydispersity as a function of time.
Source: Reproduced with permission from Ref. Magzoub (2016).

process, Fig. 12. Then, the Au salt was combined with the photo initiator in POPC liposomes, where the spherical and homogeneous gold NPs with the size (2.8 1.6 nm) and shape distributed in the aqueous core of the liposomes were synthesized under regulated conditions, Gudlur et al. (2015).

Antnia Busquets produced liposomes using the hydration of the thin film. To determine the impact of the lipid profile on the entrapment performance, several lipid compositions, including phosphatidylcholine (PC), PC/cholesterol (CHOL) (8:2), PC/phosphatidylserine (PS) (8:2), and PC/PS/CHOL (6:2:2), were utilized. then, the obtained liposomes were extruded at room temperature using a Liposofast apparatus and passed through a 200 nm pore size polycarbonate membrane filter, Fig. 13. The next step in characterizing the produced liposomes was to use a Zeta sizer to measure their size and polydispersity index. To create magneto liposomes and incorporate Fe3O4 (magnetite) nanomaterials into liposomes, stable liposomes were created. Concerning the iron concentration rather than the quantity of particles, the encapsulation was effective regardless of particle size. The liposomes' average particle diameters were all between 100 nm and 200 nm, Magzoub (2016).

In 2017, Haryono and colleagues used the thin layer evaporation approach to create the nanoliposomes by soaking phosphatidylcholine in chloroform and allowing it to evaporate, Fig. 14. To modify the thin layer of a lipid film, phosphate buffer saline (Ph 7.4) was introduced, and the mixture was vortexed for 15 min. Using nanoscale analyzer and TEM, the morphology and average particle size of liposomes were observed, Haryono et al. (2017).

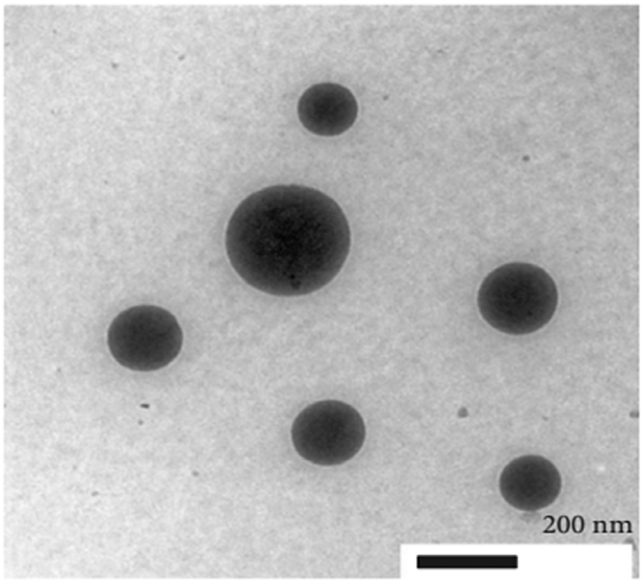

Fig. 14. TEM image of liposome nanoparticles,.
Source: Reproduced with permission from Ref. Haryono et al. (2017).

7. Application of liposomal DDs in treatment of diseases

The application of nanomaterials in biomedicine involves the construction of novel methods for clinical diagnostics, drug architecture, and drug delivery substances to increase a drug's bioavailability by subjecting them to appropriate surface improvements, where the major

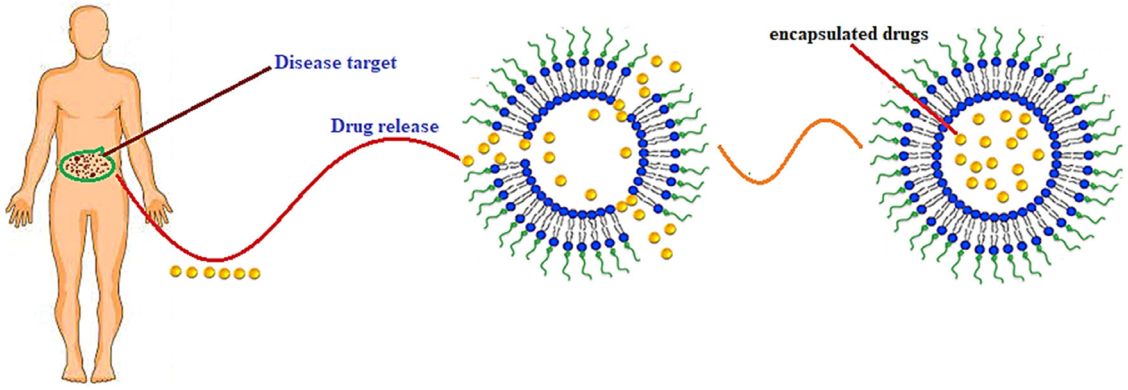

Fig. 15. Schematic entrapped liposomal DDs in treatment of diseases.

aim is to endow them with biochemical characteristics and features. Nanoliposomes are widely used for their beneficial profits in the creation of novel medications, vaccines, and tumor treatments, as well as a technique for the early identification of various illnesses, Fig. 15.

7.1. Antifungal potentialities of nanoliposomes

Across the recent generations, there has been an increase in incidence of superficial or systemic fungal diseases all over the world. Additionally, the existing approaches to treating these conditions are time-consuming and subject to negative effects, particularly when taken orally. Reaching the target location is also difficult due to the absence of bioavailability, low absorption capability, and inadequate drug delivery. A wide variety of items depending on nanotechnology have been created to address these problems. According to the excellent skin permeation potential and potency of various pharmaceuticals, phospholipid nanocarriers based on nanoliposomes, such as Amphotericin B and ciclopirox, are the most popular, Emmen and Storm (1987) and Gordon and Rifkind (1989).

7.2. Skin-curative potential of nanoliposomes

The broadest and most crucial tissue for administering systemic and tropical medications is the skin. It works by serving as a passive obstruction to the penetrant particles in order to shield the organism from the outside world. Its contact to the surroundings increases sensitivity to infection and harm. The primary shield of the skin is called the stratum corneum (SC) made up of 15 to 20 layers of murdered epidermal cells containing ceramides, cholesterol, and fatty acids. External medication administration using nanoliposomes is often used to improve the absorption of active ingredients into the epidermal layers, Sabnis et al. (2012), Franceschini et al. (1980) and Oku (2017). Since combined with SC lipids, their structure enables them to produce a drug storage, facilitating the penetration of lipophilic drugs into the skin. Of course, size is important for developing innovative nanoliposome-based drug delivery methods for epidermal and external applications. As demonstrated by microscopical research, this indicates that liposomes bigger than 0.7 micrometer cannot pass. In fact, one possible method by which external liposomal networks engage with the skin is that intact liposomes may be taken to the skin surface prior to their intracellular or intercellular excursion within the skin. Certain liposomes can also burst on the epidermis. Additionally, it should be remembered that narrower vesicles are more likely to penetrate. Furthermore, the multilamellar liposomes that lost their outer bilayers after penetrating may have given rise to the intradermally confined mono or poly vesicles, Patra et al. (2018).

8. Future perspectives

Medications based on liposomes are the first nanosized medications to be authorized for therapeutic usage. They have a recognized place in the majority of drug delivery methods with a significant impact on numerous biological fields. Liposomes have valuable uses in a variety of fields, including the delivery of drugs, genetic medicines, and imaging. These operations are made possible by their unique characteristics like biocompatibility and biodegradability, as well as nanosized configuration. Several liposomal medications and compositions are now on the market which demonstrated the importance of liposomal technology's advancements and problems in laying the foundation for upcoming study that will expand on already-established platforms. In order to enhance liposomal drug delivery, research must be done to expand the horizons of understanding in formulation and production, toxicological examination, cellular interactions, and therapeutic investigations.

9. Conclusions

For a number of disorders, liposomes have been effectively used as a reliable medication delivery mechanism. Water-insoluble, poorly accessible, and extremely lethal drug's pharmacokinetics and pharmacodynamics were improved by the biocompatible, biodegradable, and low immunogenicity liposome composition. However, the main problems with liposomes are their physicochemical longevity. As a result, discovering of new liposomal preparation methods or their developments toward the fast, sustainable, economic and simple ones are an essential need to produce stable liposomes with significantly impacts in clinical application.

CRediT authorship contribution statement

Abdulbast Ali Khafoor: Searching, Drafting, Revising. **Ayoub Sabir Karim:** Searching, Drafting, Revising. **S. Mohammad Sajadi:** Searching, Drafting, Revising.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

No data was used for the research described in the article

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All authors approved the final version of the manuscript.

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