Review Article: A Review on Phospholipid and Liposome Carriers: Synthetic Methods and Their Applications in Drug Delivery

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ABSTRACT

In drug delivery, it is attempted to keep the biocompatibility of drugs in body organs. For example, it is needed to use a high dosage of anti-cancer drugs several times, which shows side effects such as hair loss and paleness. Therefore, the researchers developed phospholipids, liposomes, and micelles as carriers, causing to delivery of drugs at defined times and organs. In phospholipids, there are hydrophile group and hydrophobe chains the hydrophobe groups of acyles are attached to alcohols and makes various phospholipids. The most common phospholipids are phosphatidyl choline, phosphatidyl ethanol amine, serine, etc. Liposomes are oily visicol in aqueous solutions. Also, liposome carriers are commercially found and the ratio of liposomes to other carriers has been reported. Micelles are comprised of oils in aqueous media. The co-chelating agents are divalent phospholipids of natural materials that are potent in the delivery of fungicides, protein, etc. Microgels are three-dimensional polymer networks colloidal gels. Hydrogels, another candidate for controlled drug release, have a special application in the field of controlled drug release, due to their high internal free volume with high fractions of loaded drugs.

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1. Introduction

In drug delivery, efforts are made to increase the amount of bioavailability of drugs in specific tissues, or organs of the body, and at specific times. This work is given a lot of attention to new pharmaceuticals. In addition to the advancement of knowledge and different sciences, the knowledge boundaries are becoming blurred, have reached, and in some fields, we are witnessing the fusion of different sciences. One of these important, applied, and extensive fields is "engineering of drug release systems" which has a common border with many sciences including biomaterial engineering, and clinical engineering, it has mathematics, histology, biology, and pharmacology. This field is one of the most modern topics presented in today's world

sciences, which has been accompanied by advances in optics, and today it has made a major contribution to the research of engineers, especially engineers in biometrics [1, 2].

1.1. Modern drug delivery

In modern drug delivery methods, small amounts of the active ingredient are delivered to the target point by appropriate carriers. The application of nano-carriers in modern drug delivery systems is an important practical method to reduce side effects in cancer treatments, which are used in the form of dendrimer, micelles, hydrogels, metal-organic, and inorganic nanostructures, polymers, and nano-liposomes [3].

1.1.1. Gastro retentive drug delivery systems

Recently, the development of various gastro retentive drug delivery system (GRDDS), such as magnetic field-assisted gastro-retention, plug type swelling system, mucoadhesion technique, and floating system were employed. The size, density, and physiological factors like extrinsic and biological factors are the main factors which affect on Gastro retention [4, 5].

The merits of GRDDS are as presented as follows [6, 7].

• The floating dosage form is advantageous for producing local action in the stomach.

• It is possible to get targeted and controlled drug delivery.

• Gastro-retentive dosage form minimizes the fluctuation of drug concentration [6].

The demerits of GRDDS are illustrated as follows [8, 9].

• Some drugs may produce gastric irritation which are not desired.

• The hydration state of the dosage forms the impact on the ability to float.

For the drugs having limited acid solubility the system is not suitable.

1.1.2. Floating drug delivery system (Low-density system)

This system releases the drug slowly at the desired rate when the dosage form floats on the gastric fluid contents, through which gastric retention time and plasma drug concentration can be increased and maintained. Floating drug delivery systems were developed under two different systems [6].

1.1.2.1. Non-effervescent system

It is also called Hydrodynamically Balanced System (HBS). This system stays buoyant through the air entrapment in the swelled polymer. When this system contacts the gastric fluid, the hydrocolloids hydration occurs by forming a gel on the surface and ultimately controls the drug release. As the outer surface goes into the solution, a barrier layer of gel is maintained immediately by an adjacent hydrocolloid layer [10].

1.1.2.2. Effervescent system

In this system, swellable polymer and effervescent components are used and the floating is formed in the stomach by incorporating a floating chamber. The matrices are formulated so that they liberate carbon dioxide in the stomach due to the acidic environment. These systems were divided into a volatile liquid-containing system and a gas-generating system [11, 12].

1.1.3. Soft drugs (SDS)

Soft Drugs (SDs) are organically active drugs and careful to take a foreseeableand controllable absorption near harmless besides sedentary foodstuffs. Consequently, they consume their anticipated pharmacological consequence [13]. The molecule could stay disabled, and then be disinfected shortly after it has drilled its biological effect [14]. Samples of soft drugs are hallucinogens like cannabis [15], mescaline, psilocybin [16], lysergic acid diethylamide (LSD) [17], ayahuasca [18], and dimethyltryptamine [19]. Given that medicines are not perfectly prepared as correspondingly soft, or hard drugs, and have physiognomies of both. Examples of such drugs are 3,4-methylenedioxy methamphetamine [20], ketamine [21], phenyl

cyclohexyl piperidine (PCP)[22], dextromethorphan (DXM) [23], synthetic cannabis, and caffeine [24]. Consequently, these canisters remain definite as medicines which remain crop predictable and manageable *in vivo* metabolism to form nontoxic crops. Hence, they consume them, exposing their sustaining role [15] among which acetyl pyridinium chlorides, and soft chloramine are mentioned**.**

1.1.4. Pharmaceutical application of prodrugs to elevate patient satisfactoriness

A prodrug is an organic matter without pharmacological motion, but metabolically altered and addicted to a compound through the anticipated motion. Prodrugs can be exploited for the variability of resolutions, together with enhancing bioavailability or pharmacokinetics of a medicine, diminishing medication harmfulness, simplifying management of the medication, or transporting the medication to detailed cells or tissues [25].

1.2. Controlled drug delivery system and its importance

What comes to mind after hearing the name of the medicine for the first time, it is probably nothing more than a pill, capsule, or ampoule. Medicines come into two digestive ways (entering through the mouth and being absorbed into the blood along the digestive tract) and non-digestive injections, eye drops, etc. enter the body. While the world of medicine and the methods of its transfer to the body are not limited to these two methods. Therefore, researchers are looking for a solution that can solve the above problems to a great extent. Following these efforts, controlled drug release systems were proposed, which have many advantages. The most important advantages include the ability to maintain the drug concentration for a certain period, the possibility of delivering the drug to a specific organ or tissue, and the ability to adjust the speed of drug release depending on the place of drug delivery, liposome, noisome, ceramic, or metal are combined with medicine or active agent in a calculated manner so that the active agent is released from this substance in a predetermined way in the body [1, 2].

1.3. Drug delivery by nanocarriers

In recent years, much attention has been paid to the use of nanoparticles as medicinal carriers. Nanoparticles are colloidal carriers that can be of natural or artificial origin, and their size is usually between 1 and 1000 nm. Polymeric materials such as polyamide, and amine, or mineral materials such as gold are prepared. These carriers existed in the form of nanocapsules and nanospheres can absorb and encapsulate various drugs, thus protecting the drug against degradation. and lead to different tissues and cells. Nanocapsules are vesicle systems where the drug is enclosed in a colloid cavity and surrounded by a polymeric membrane, while in nanospheres, the drug is physically and uniformly dispersed in the polymeric matrix. There are other types of colloids which are not nano-like liposomes and micelles which are widely used for drug delivery to the body. Of course, these carriers are separated from the polymer and inorganic nanocarriers due to their unique characteristics. Drug delivery systems based on nanocarriers have now entered the world pharmaceutical market and their use in drug delivery is increasing day by day [1, 2].

As mentioned in the previous sections, the nanoparticulate drug delivery systems include liposomes [26], polymeric micelles [27], polymeric nanoparticles [28], gold [29], silver [30], silica [31], and other metal nanoparticles. The pH and temperature are the primary factors studied in drug delivery systems [32]. Any imbalance in body pH or temperature may alter the immune response and lead to autoimmune diseases, infectious diseases, cancer, and diabetes or Parkinson's disease. The researchers are going to develop thermo, and pH dual stimuli-responsive polymeric nanomaterials, or micelles for cancer treatment [33].

1.4. Common drug release systems

Common drug release systems include tablets, capsules, creams, ointments, solutions, suspended particles (suspensions and

emulsions), and injection systems. Using these drug delivery systems with alternating doses causes fluctuations. The drug concentration in the blood is sometimes noticeable between two toxic and therapeutic limits. In addition to this problem, issues such as the injection pain and the problem of swallowing pills by some patients led to the attention of the appropriate methods of drug transfer. The therapeutic level of the drug should in the patient, it should be enough to take the next dose of the drug to meet the patient's need. But unfortunately, it is observed that the excess reduction or increase of the drug affects its effectiveness. In these cases, the body increases the amount of drug in the blood circulation system or the injection site, which causes toxicity in some drugs. Therefore, the slow and controlled drug release technologies aim to control the drug release rate and target the release of the drug to, of course, the use of these systems with limitations that may include the emergence of new toxicities due to carry fresh substances in the body along with drugs, delay in drug dispersion, and the need for new tests to check the drug carrier [1, 2].

Drug release is a set of operations, formulations, techniques, and systems used to deliver a combined drug in the body to secure the treatment effect, action in any case, the amount and duration of drug release, and the quality of release are usually important. Drug release is usually presented through the chemical formula of the drug, but it may include medical drugs or combined drugs. Drug release is a concept that depends on the intensity and dosage, and thus the penetration method is defined. Delivery technologies as well as comfort and patient care are effective. Drug release is based on the process of diffusion, swelling, destruction, distribution and prescription, etc. The most common methods of drug administration in this way are oral (oral), topical (skin), transmucosal (vaginal, buccal/subcutaneous, nasal, subcutaneous, eye, and rectal), and inhalation routes. Many drugs such as peptides, protein, and gene-based drugs, in general, may not be released by using these methods because they may be sensitive to enzymatic degradation, or due to issues related to molecular size and charge at the therapeutic level, not be effective. Therefore, many proteins and peptide drugs should be released by injection or by nanoparticle makeup. For example, many vaccines work based on the release of protein drugs and often by injection. Current efforts in the field of drug delivery include the development of targeted delivery, in which the drug acts only in the target area of the body (for example, in cancerous tissues). The release formulation and the stability of the drug during the experimental period and the controlled time. The release of the drug depends on the formulation and the methods of increasing the retention of the released agent, in which the drug should pass through the acidic environment of the stomach. To achieve effective goals, the targeted system should be designed in such a way that avoids the defence mechanisms of the host and reaches the target location [1, 2].

2. Discussion

2.1. Phospholipids and their applications in drug release systems

Phospholipids are molecules in which hydrophilic head groups and hydrophobic acyl chains are attached to alcohol and create a wide spectrum of phospholipids. (DDS) is difficult [34]. Phospholipids have special properties such as high biocompatibility and bi-friendliness, emulsification, and friability. Phospholipids are lipids with phosphorus, a polar part, and a non-polar part, which can be divided into two groups: glycerophospholipids and sphingomyelins [34].

2.2. Glycerophospholipids

Glycerophospholipids are the main phospholipids in which glycerol forms the main structure. All natural phospholipids have an alpha structure and an L configuration, glycerol, and the number of aliphatic chains to be classified [35].

2.3. Glycerophospholipids (GPLs) and phospholipids.

Phospholipids are a type of complex lipids, the molecular skeleton of which is glycerol (glycerophospholipids), or the long-chain amino alcohol sphingosine (phosphosphingolipids). **Figure 1** displays the scheme of glycerophospholipids and the scheme of phospholipids are depicted in **Figures 1** and **2**. GPLs present in the membranes of all cell types, but the content of individual phospholipid classes depends on the type of tissue. Phosphatidylcholine (PC) is the main constituent of phospholipids (40–50%), but it is mainly presented in the outer layer of the cells. In the inner layer, phosphatidylethanolamine (PE, approximately 20–30% of all phospholipids) and phosphatidylserine (PS, approximately 5–10% of all phospholipids) predominate. Phosphatidylinositol (PI) makes up 1–10% of all phospholipids and is mainly found inside cell. It is most often employed as a precursor to many PI phosphates, which are involved in various cell signaling processes [36].

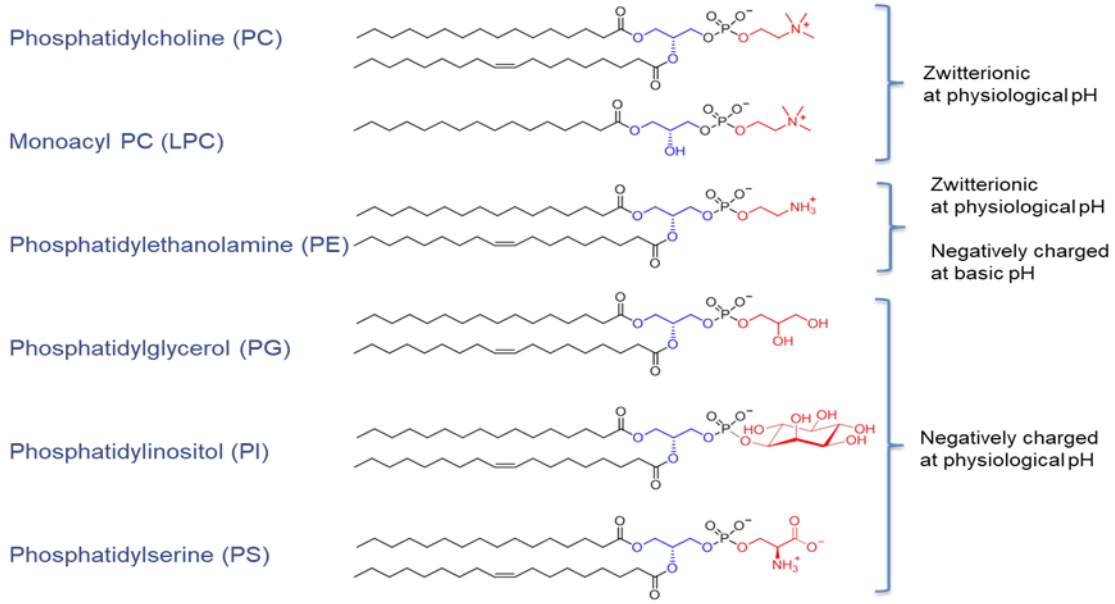

Figure 1. Types of glycerophospholipids and phospholipids [37]

2.4. Sphingomyelin

Sphingomyelin is an important component of animal cell membranes, which was identified in 1884, and proved in 1927 that the structure of this compound is -N-acyl sphingosine-1-phosphatidyl choline. All SMs are D-erythro configuration. Although phosphatidylcholine (PC) and SMs are very similar in terms of structure, but they have differences as follow:

1. The main chain of SM structure is sphingosine, while the main structure of phosphatidylcholine (PC) is glycerol.

2. The number of cis double bonds in acyl chains in PC molecules is about ten times more than in SM molecules.

3. The acyl length of naturally occurring SMs is usually more than 20, while the paraffin residues of sphingosines are relatively short, so SMs are asymmetric molecules [38].

2.5. The main sources of phospholipids

According to the sources, phospholipids can be divided into two types: natural and synthetic.

Natural phospholipids were initially identified in complex aliphatic compounds in 1793, and later phospholipids were discovered in the human brain in 1812 and egg yolk in 1846. The word lecithin was primarily used to describe the viscous orange substance isolated from egg yolk. The chicken was used. After 20 years, the choline component in lecithin was diagnosed. The main sources of phospholipids include vegetable oils (soybean, cottonseed, corn, sunflower, and rapeseed) and animal tissue (eggs yolk and cow marrow). Egg yolk and soybean are the most

important sources of phospholipids, and their differences are as follows:

1. Egg yolk lecithin has more PC.

2. Egg yolk phospholipids have unsaturated and long-chain fatty acids, mainly arachidonic acid (AA) and docosahexaenoic acid (DHA), which are not presented in soybean lecithins.

3. Animal lecithins have characteristics due to the SM presence.

4. The saturation level of egg yolk lecithins is higher than soybean lecithins and they have better oxidation stability.

5. The cost of natural phospholipids is lower than the synthetic or semi-synthetic types, but the purer the natural phospholipids are, the more expensive they are [39].

2.6. Synthetic phospholipids

The phospholipids synthesis includes two methods: semi-synthetic and complete synthesis. In the semi-synthetic method of glycerophospholipids, it refers to the change of head, tail, or both groups in natural phospholipids. Therefore, the semi-synthetic method, compared to the full synthesis method, requires fewer reaction steps. The semi-synthetic methods of glycerophospholipids are mainly as follow:

1. Double bonds of natural phospholipids are hydrogenated to obtain saturated phospholipids with higher melting temperatures and oxidative stability.

2. Deacylation of natural PC, with activated acyl derivative- acylates glycerol-3-phosphocol GP) and creates the desired PC.

3. Phospholipase D catalyzes glycerophospholipids to produce phosphatidic acid (PA). Hydroxy acceptors (glycerol and serine) can bind to PA to convert the choline headgroup into various phosphorylated alcohol headgroups. Complete synthesis glycerophospholipids are in the form of ester or ether bonds attached to the non-polar part of the glycerol chain and the head bond is polar. Synthetic glycerophospholipids have advantages such as single components and stable properties. The natural semi-synthetic process to obtain SM includes the deacylation of SM extract sphingosine phosphocholine, which is then obtained by the desired fatty acid. It has been found that during SM, are acylated until the deacylation-reacylation process, a large amount of L-trieo isomer is formed, which is the final product of a mixture of D-erythro and L-trieo isomers [40].

2.7. Physiological properties of phospholipids

Phospholipids are essential components of all cellular and subcellular membranes and widely distributed in humans, animals, plants, etc. They can be arranged in a way to form a double-layer membrane. In addition, to create membranes, phospholipids, and lipoproteins, they gather the scattered particles together, whose the main function is to transport lipophilic triglycerides and hydrophilic cholesterols in the blood. In the human body, phospholipids are emulsifying agents. Phospholipids together with cholesterols and bile acids form mixed micelles to compile the gallbladder for increasing the absorption of fat-soluble substances. Also, the human body uses phospholipids as surfactants in the lungs, the outer membrane of the heart, joints, etc [41].

2.8. Physical properties of phospholipids

Polymorphous phospholipids in water can form different types of assemblies such as micelles, liposomes, and hexagonal phase (HII) which depend on the molecular shapes of phospholipids and have different physical properties. Polymorph lipid regulation factors non-bilayer lipids, such as unsaturated PE, can be stabilized in a bilayer structure by the lipids presence such as PS which prefer a bilayer structure. It has been determined that between 20% and 50% by mole of bilayer lipids is required when with lipids with a hexagonal structure (HII) like PE, they are mixed to maintain the double layer structure. Structural priorities in these systems can be adjusted by various factors such as head group size, temperature, hydrocarbon unsaturation, ionic strength, formation of inverted cone molecules,

and the presence of divalent cations such as Ca^{2+} [42].

2.9. History of liposomes

Liposomes are colloidal particles with a membrane of two or more phospholipid layers, which have been the subject of extensive research for researchers interested in this field for more than 45 years. The possibility of the presence of vesicle-like structures in aqueous systems containing amphiphilic molecules was intially reported by Barnard, Barnhardt, and Barnard. Microscopic studies of the forms of myelin made by ammonium oleate in water were assumed in 1974. In 1962, Bingham and R.V. Hume's colleagues, by using an electron microscope in Cambridge, demonstrated the phospholipids dispersion in water by using a negative staining. They investigated sodium phosphotungstate and ammonium molybdate, and the evidence of their final experiments showed that phospholipid forms a bag-like structure through self-assembly, which Gerald Wiseman called liposomes [43].

2.10. Liposome

Liposomes are pits prepared with phospholipids as the main material, whose structure is similar to the cell membrane. Liposomes as drug delivery carriers have advantages such as lipophilic and hydrophilic drug delivery, controlled release properties, cell affinity, they have tissue compatibility, reduction of drug toxicity, and improvement of drug stability. Liposomes can be used as carriers of antitumor, antifungal, analgesic, gene therapy, and vaccines [44].

The liposome is a microscopic vesicle containing a phospholipid bilayer that surrounds a liquid space. The thickness of this lipid bilayer is usually between 3 nanometers and 6 micrometers. Likewise, the liposomes formed by them can have a diameter between 50 nanometers and 50 micrometers. Due to the amphipathic properties of its components, liposomes provide the possibility of simultaneous delivery of hydrophilic (water-loving) and lipophilic (fat-loving) drugs. Features such as low inherent toxicity, biodegradability, and biodegradability have caused liposomes to be considered a very suitable carrier in modern drug delivery systems. These small and bag-like structures are similar to packages or capsules placed in the inner tubes without using them to carry drugs to different parts of the body. As a result, drug delivery is one of the important applications of liposomes.

Phospholipid vesicles or liposomes are colloidal particles with two or more phospholipid membranes that are important as drug carriers in modern drug delivery systems. Even now, the possibility of engineering a wide range of different sizes, phospholipid composition, and surface features has been developed. Many different methods have been developed for the liposomes preparation, the two general methods of liposomes preparation based on drug loading in them are (i) active loading techniques and (ii) inactive loading techniques. Depending on the goals of the work, it is different. He modified liposomes with different molecules and polymers and created a special feature. Nowadays, there are various applications for liposomes. The biocompatibility and ability to carry hydrophilic and lipophilic drugs together have made them as one of the most desirable carriers in the new drug delivery system. Nowadays, new anticancer drugs such as daunorubicin and doxorubicin used liposomes as a drug carriers have found clinical use [44].

2.11. Structural features of liposomes

The liposomes structure reflects some of their unique properties in drug delivery. Therefore, knowing the liposomes structure helps to better understand the mechanism of action of liposomes, the strengths, and weaknesses of this new drug delivery system. Liposomes are bags consisting of double-layer lipids that are produced artificially. The liposomes structure is made up of amphipathic molecules with one hydrophilic and one hydrophobic. Since most of the synthesized liposomes are formed from amphipathic lipid molecules called phospholipids, the phospholipids structure consists of an alcohol group as a phospholipid

skeleton, glycerol, sphingosine, or two fatty acid molecules, a phosphate group and phosphate-related groups. Phospholipids have amphipathic properties. One end of them has a phosphate group (hydrophilic) and the other has a fatty acid (it is hydrophobic because of the hydrocarbon structure).

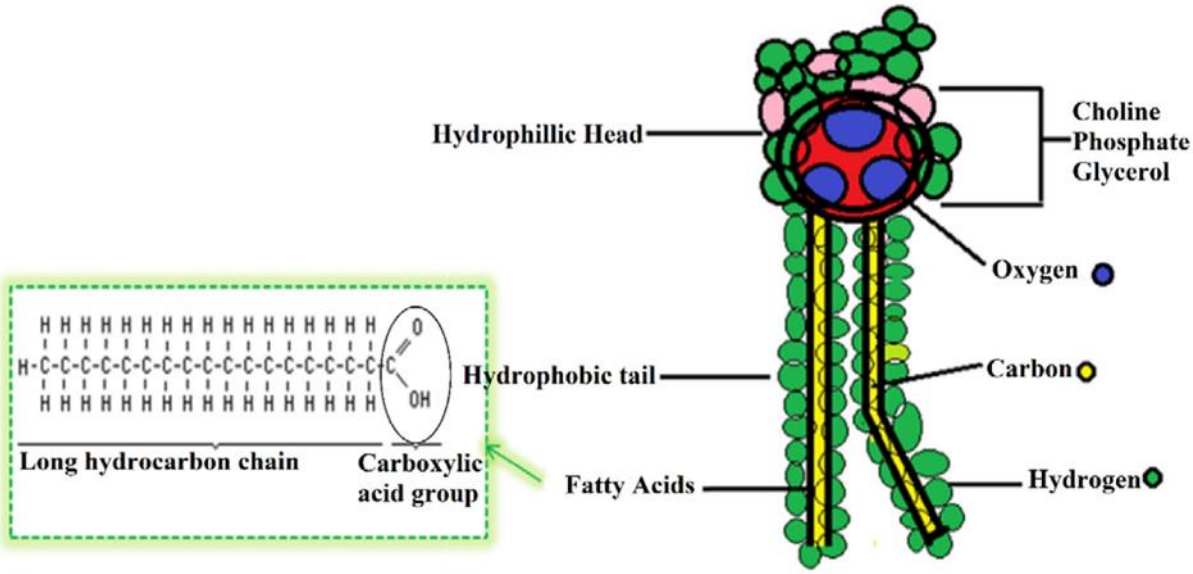

Figure 2. Scheme of phospholipids structure [45]

Phospholipid vesicles or liposomes are formed from the association of these phospholipids in a fluid environment. Of course, cholesterol is also added in most cases to control the membrane fluidity and stabilize the synthetic liposomes. The scheme of a liposome is demonstrated in **Figure 3**.

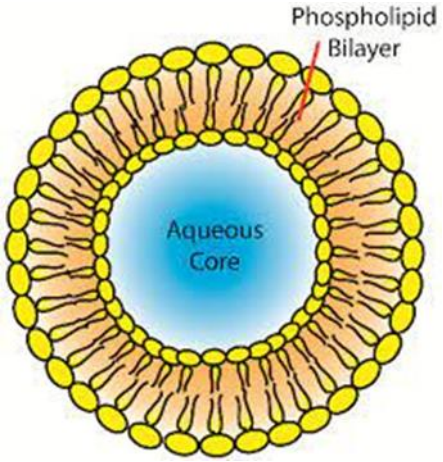

Figure 3. The schematic of liposome

In chemical and physical conditions, liposomes have many characteristics and characteristics of colloidal particles. Currently, it is possible to engineer a wide spectrum of size, phospholipid composition, and surface characteristics of liposomes. Two layers and also by combining and covalent bonding with proteins (such as antibodies and proteins related to sugars such as lectin) and modified glycoproteins and synthetic proteins.

2.12. Liposome synthesis methods

In the liposomes synthesis for drug delivery systems, two important goals are considered. First, the synthesis of the considered liposomes and second, the efficiency of putting the drug

inside them, or in other words, loading the drug inside the liposomes.

Many different methods for the liposomes preparation have been invented and developed (**Table 1**) , but a limited number of them can hold large amounts of drugs dissolved in water. Here, a question arises among the types of liposome synthesis methods, which method is more appropriate?

Figure 5 illustrates the liposomes scheme based on structural parameters. On the one hand, it is a more appropriate method to produce liposomes of the desired size and on the other hand, and to have a good drug loading efficiency. Therefore, the choice of the synthesis method is very important. The choice of a method for liposome preparation depends on the following factors [46]:

1. The physicochemical properties of constituents of liposome.

2. The media in which lipid vesicles are scattered.

3. The potential toxicity of liposome.

4. Additional processes involved during the use or delivery of vesicles.

5. Optimum size, polydispersity, and shelf-life for vesicles for application purposes.

Table 1. Summary of the synthesis steps of liposomes [47]

Explanation	Synthesis steps
First, fat molecules or phospholipids is dissolved in an organic solvent. Then, the organic solution is replaced with an aqueous solution. As a result, the organic solvent containing fat or phospholipid molecules is removed from the solution medium by evaporation. It is done by a rotary.	1- Drying fat from organic solvent
At this stage, the aqueous solution is replaced with an organic solution so that the fat molecules are dispersed in this environment and form various liposomes with different dimensions and layers.	2- Dispersion of fat in water environment
Now liposomes with desired size and type should be purified from various synthetic products.	3- Purification of the resulting liposomes
Finally, the properties of the purified liposomes is identified by different techniques.	4- Analysis of final products

2.13. General methods of liposome preparation based on drug loading

There are two gereneral methods for this regard: active and passive loading techniques. In the passive loading techniques (**Table 2**), drugs are trapped before or during liposome production. This method is divided into three groups, each of which includes different techniques. In these techniques, aquatic drugs are presented in the environment. They are encapsulated in liposomes and hydrophobic (fat-loving) drugs are trapped between two phospholipid layers. For example, water-soluble drugs are added to an aqueous solution, which is trapped between the mass and aggregation of hydrophobic heads, and the lipid-soluble substances in between phospholipid bilayers are replaced [49]. **Figure 4** indicates the encapsulation scheme of the drug inside the liposomes.

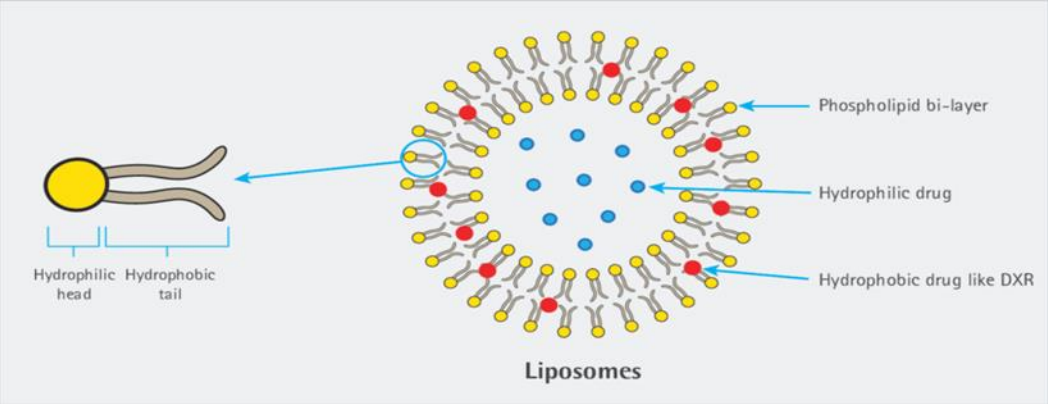

Figure 4. The scheme of encapsulation of the drug inside the liposomes

When water-soluble drugs are enclosed in liposomes, they do not change the physical properties of the liposome, and there is no interaction between the drug and the liposome. However, when the liposome drugs are placed in the liposome membrane, it causes significant changes in their physical properties such as the phase transition temperature (TC). The liquid is transformed into phase change temperature (TC).

Table 2. Various methods of loading liposomes [49]

Lipid film hydration by hand shaking, free-hand shaking, or freeze drying.	1- Mechanical diffusion methods	1-Passive loading techniques
Micro- emulsification		
Sonication		
French pressure cell		
Membrane extrusion		
Dried reconstituted vesicles		
Freeze- thawed liposome		
Ethanol injection	2-Solvent diffusion methods	1-Passive loading techniques
Ether injection		
Double emulsion		
Reverse phase evaporation vesicles		
Stable multilamellar vesicles		
Detergent (cholat, alkyl glycoside) removal from mixed micelles by dialysis, column chromatography, and dilution	3-Detergent elimination methods	

Active loading techniques are related to a specific type of compound with ionized groups or compounds that are soluble in both water and fat and can penetrate liposomes after their formation. For example, drugs have a dual nature, they can easily penetrate the liposomes

after they are formed and be loaded inside them. It should be noted that in inactive loading techniques, drugs are trapped inside the liposomes before or during their formation. they fall and after the formation of liposomes, they cannot penetrate them. As a result, active loading techniques are limited to the restricted drugs [49].

2.14. Modifying liposomes surface

For different applications, liposomes with different characteristics are needed. To obtain liposomes with distinctive and desirable characteristics, this goal can be achieved to some extent by modifying their surface. By modifying the surface and obtaining new characteristics, the liposomes spectrum as a carrier in modern drug delivery systems has been widely expanded. The liposomes surface can be coated with different types of natural substances such as glycolipids, and glycoproteins, or by using chemical bonding, modify with other molecules, especially macromolecules such as proteins such as antibodies, lectin, or synthetic polymers such as polyethylene glycol or polylactic acid to achieve various goals. The connection of polymers or macromolecules to the liposomes surface is of the type of chemical connections (covalent bond) or the type of physical connections (Vander Waals or hydrophobic, etc.), depending on the type of polymers or macromolecules at the surface and levels. There is an end to them [50].

2.15. Surface modification of liposomes

Different materials are used for modification of the liposome surface, as represented in **Table 3**. One of the suitable methods for modifying the surface of liposomes are PEGylation, in that the liposome surface is conjugated with poly(ethylene glycol) (PEG). PEGylation prevents non-specific protein adsorption and phagocytosis, thereby prolonging the blood residence time. However, PEGylation cannot fully inhibit protein adsorption or protein corona formation on liposomes. PEGylated liposomes are rapidly cleared from the circulation upon repeated doses through accelerated blood clearance **[51-53].**

Table 3. Types of surface modification of liposome [54]

Materials	Purpose	Surface modification
1- Gangliosides GM1, GD1a	To bind antibodies.	Glycolipids
2- Gangliosides GD1b, GD1a, and GM1		
3- Gangliosides GT1, GD1a, and GM1		
4- Ceriroside sulfates		
1-Glycophorins	Used for precise targeting. These surface glycoproteins are used to bind with cell surface receptors.	Glycoproteins
2- Viral rod glycoproteins (virosomes)		
Immunoliposomes (liposomes with antibodies)	Used for accurate and active targeting.	Antibodies (immunoliposomes)
Manoz	Liposome stability by reducing their oxidation, on the other hand, increasing the stimulation of the blood endothelial system (suitable for adding to vaccines to	Polysaccharides

	further stimulate the immune system).	
	To bind to cell surface receptors.	Panties
Polyethylene glycol (PEG)	To increase plasma half-life and reduce immunogenicity.	Synthetic polymers

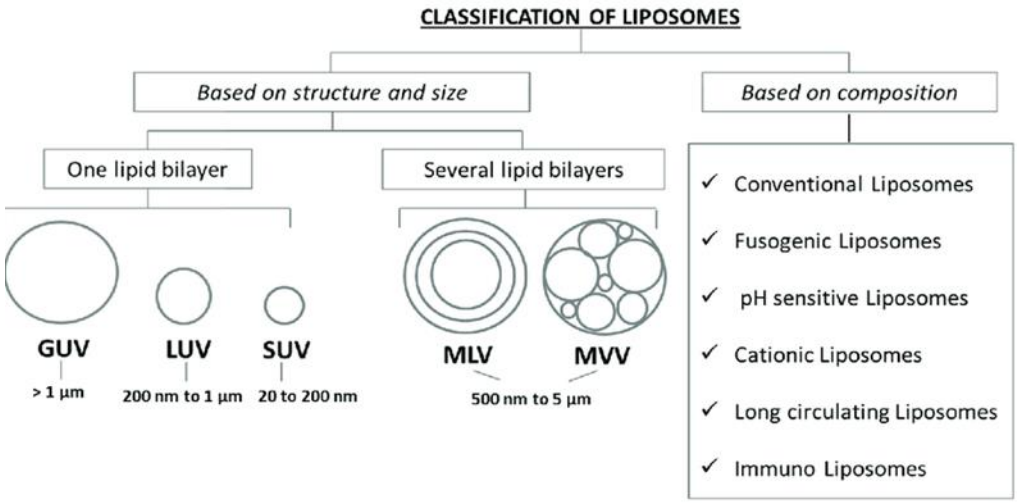

Figure 5. Schematic of liposomes based on structural parameters [55]

2.17. Advantages and disadvantages of liposomes

2.17.1. Advantages

1. The physical trapping of the drug, causes the site of the drug's effect to remain unchanged.

2. High drug loading capacity and no effect on the general characteristics of the drug carrier.

3. The drug inside these liposomal carriers is protected from the sting of enzymatic degradation.

4. It can carry both water-soluble and fat-soluble drugs.

4. Liposomal carriers are biodegradable and non-toxic.

5. Liposomes can be in the form of suspension, aerosol, semi-solid, and powder [56].

2.17.2. Disadvantages

1. It cannot pass through the integumentary barrier, so it has difficulty reaching the tissue.

2. It is recognized and swallowed as a foreign particle by the reticular system of the inner body.

3. They have a slow drug release, which is a challenge for anti-cancer drugs because it causes drug resistance.

4. The production price of liposomes is very high.

5. They have a short half-life.

6. Only a few of them are stable [57].

2.18. Micelles

Micelle MCBIN introduced the term "micelle" in 1913, which are colloidal grains formed by mixing detergents in water (liquid colloid). They are amphiphilic molecules with a nonpolar

(hydrophobic) tail facing the center and a polar (hydrophilic) head in contact with the external solvent (**Figure 6**). Likewise, reverse micelles can be obtained by the amphiphile or detergent molecule in a nonpolar solvent, producing micelles with the head and tail centers facing outward. The condition of the solution (temperature, ionic strength, and pH) and the nature of the amphiphilic molecule determine the size and shape of the produced micelle nanoparticles. The critical micelle concentration (surfactant concentration) determines the proper micelle formation. Below the critical micelle concentration, proper micelle formation will not occur. Along with amphiphilic molecules, polymer micelles are formed in certain solvents with the help of two copolymers. One of the copolymers is soluble in the solvent and the other is insoluble in the solvent. The insoluble copolymer forms the core and the soluble copolymer forms the shell in which the copolymer forms micellar chains or beads [58].

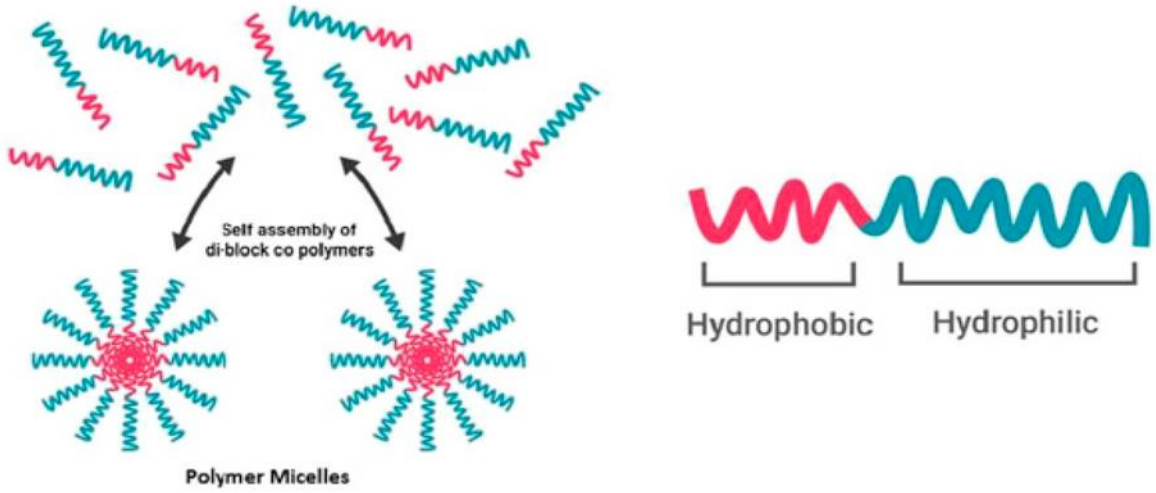

Figure 6. The scheme of micelle nanocarrier

2.19. Phospholipid-drug complexes

Many synthetic and herbal drugs have poor bioavailability problems due to low solubility in water or weak penetration in biological membranes and are not effective in treatment. If the drug concentration in the digestive tract fluid is not appropriate, it is not effectively transported and absorption decreases. Although most bioactive molecules of plants are biologically polar or soluble in water, it is difficult for them to pass through the lipid biomembrane due to their high molecular weight and low-fat solubility. Studies have shown that natural flavonoids have a special affinity for phospholipids. They can form complexes with different biological properties and medicinal activities from the parent drugs. Therefore, nowadays phospholipid-drug complexes or phytosomes are of great interest. Phytosomes are characterized by amphiphilicity, which makes them better soluble in digestive fluid and better absorbed from the lipophilic membrane system or tissue (**Figure 7**). Phospholipid-drug complexes can modify the biocompatibility of parent drugs that dissolve Their tolerance in water or fat is weak. Hence, two types of drugs can be complexed to improve biopharmaceutical properties. In addition, to enhance drug absorption, phospholipid-drug complexes have the advantage of increasing the drugs stability and prolonging the effect of drugs. The most important differences between phytosomes and liposomes are as follow:

1. The size of liposomes is much larger than phytosomes.

2. New bonds are formed in phytosomes, while no chemical bonds are formed in liposomes[59].

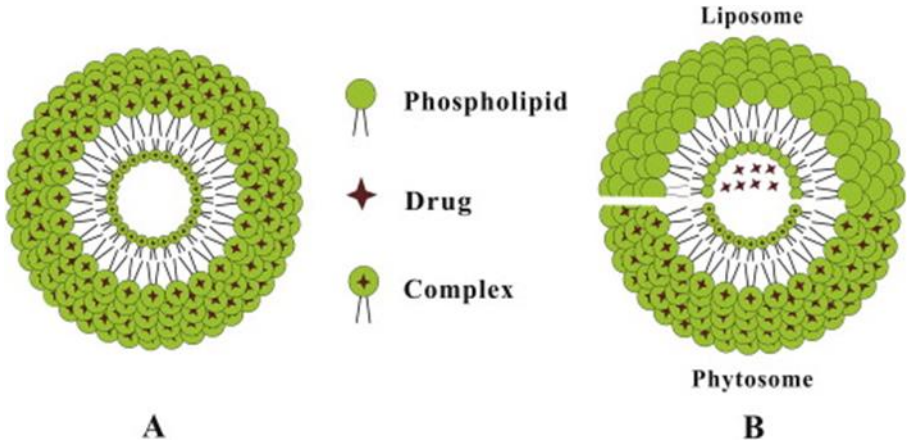

Figure 7. A view of the liposome structure (on the right) and the main difference between liposome and phytosome (on the left) [60]

3. Conclusion

In modern pharmaceutical systems, liposomes and nanoliposomes have been able to occupy a large part of the research. The use of such structures due to their similarity with biological membranes, and also their targeting has been able to improve the effectiveness of the drug and reduce on the other hand, with the controlled release of the drug in the target tissues, a greater amount of the drug will reach the target cells and the treatment process will take place at a faster rate.

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