REVIEW ARTICLE

Liposomes as a Novel Drug Delivery System: Fundamental and Pharmaceutical Application

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Abstract

Liposomes are spherical vesicles consisting of one or more phospholipid bilayers, which are under extensive investigation as drug carriers for improving the delivery of bioactive agents and many different compounds in biological, pharmaceutical, and medical and nutritional research. The majority of those clinically approved have diameters of 50–300 nm. Among several talented new drug delivery systems, liposomes characterize an advanced technology to deliver active molecules to the site of action and reduce undesirable side effects improving its *in vitro* and *in vivo* activity, as well as reducing the toxicity of the drug and enhancing the efficacy of the encapsulated drug. The present review will briefly explain the characteristics, advantages, scalable techniques based on the type of produced liposomes and potential applications of liposomes in food, cosmetics, gen genetic engineering, immunology, cancer therapy, infection, and also the diagnosis.

Key words: Liposome, novel drug delivery, pharmaceutical application

DEFINITION AND HISTORY

Liposomes are close colloidal structures consisting of one or more concentric spheres of lipid bilayers enclosing aqueous compartments. Liposomes have been attracting increasing attention as a drug carrier for drug delivery systems (DDSs) because they can carry both hydrophilic compounds[1,2] (carboxyfluorescein[3] and sodium fluorescein)[4] and lipophilic compounds (retinoic acid,[5] and tretinoin).[6] Liposomes were first made synthetically in England in 1961 by Bangham *et al.*, who displayed when phospholipids are hydrated in aqueous solution, they impulsively form closed structures. Such vesicles, composed of one or more phospholipid bilayer membranes, can trap aqueous or lipid drugs, depending on the nature of those drugs.[7] The present review will briefly express the characteristics, advantages, the preparation method and the application of liposomes in various fields.

STRUCTURE AND CHARACTERISTICS

The main part of the liposomes are phospholipids, which are amphiphilic molecules containing water-soluble hydrophilic head section and a lipid-soluble hydrophobic tail. Usually, liposomes are composed of cholesterol and phospholipids [Figure 1]. This special structure of the liposomes creates unique properties in them such as self-sealing in aqueous media and makes them ideal carrier systems with applications in different fields including medicine, immunology, diagnostics, cosmetics, ecology, cleansing, and the food industry.[8] The properties of liposomes are influenced by various factors, including lipid composition, surface charge, size, and the method of preparation.[9] Liposomes can be formed from naturally-derived phospholipids with mixed lipid chains (like egg phosphatidylethanolamine), or of pure surfactant components like DOPE (dioleoylphosphatidylethanolamine).[10] The choice of bilayer components determines the "rigidity"

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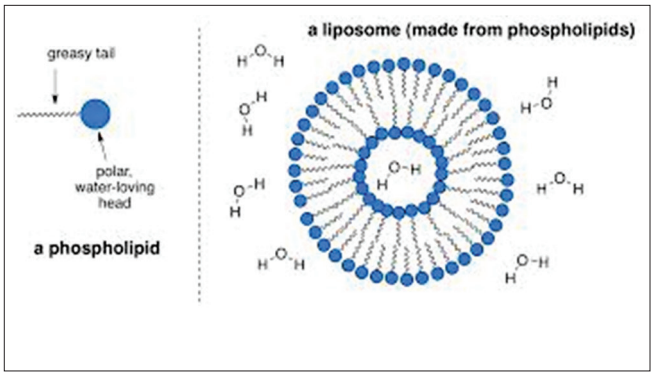

Figure 1: Scheme of a liposome formed by phospholipids in an aqueous solution

or "fluidity" and the charge of the bilayer. For instance, unsaturated phosphatidylcholine species from natural sources (egg or soybean phosphatidylcholine) is more permeable and resilient than saturated phospholipids with long acyl chains (for example, dipalmitoylphosphatidylcholine).[11,12]

CLASSIFICATION OF LIPOSOMES

Liposomes are classified based on vesicle size, number of lamella and preparation method. The vesicle size is an acute parameter in determining the circulation half-life of liposomes, and both size and number of bilayers affect the amount of drug encapsulation in the liposomes [Table 1].[13]

Liposomes are structurally divided into several categories:

Multilamellar liposomes

Multilamellar vesicle (MLV) is a liposome composed of a number of concentric lipidic bilayers with size range 0.1–0.5 μm. MLVs have onion structure. Their main advantage is that they are easy to form and have a stable building. The major disadvantage of these liposomes is limited space for loading compounds. Because more interior space is surrounded by the number of concentric lipidic bilayers, the volume available for loading the material is limited and the large size of these liposomes also limits their injectable use.[14,15]

Unilamellar liposomes

Unilamellar vesicles have a single phospholipid bilayer sphere enclosing aqueous solution. Unilamellar vesicles can be divided into small unilamellar vesicles (SUV), which their size range is 0.02–0.05 μm. These vesicles, due to their small size, are not removed from the bloodstream. Therefore, they have a greater chance of entering the tissues and showing therapeutic effects and the large unilamellar vesicle (LUV) size range varies from 0.06 um and greater, which has a lot of space to load the compounds.

Table 1: Classification of liposome-based on size and structure

Types of liposomes based on Structural parameters	Size (μm)
Multilamellar liposome (MLV)	0.1–0.5 μm
Unilamellar liposome	
Small Unilamellar liposome (SUV)	0.02–0.05 μm
Large Unilamellar liposome (LUV)	more than 0.06 um
Multivesicular liposome (MVV)	2–40 um
Oligolamellar liposome	0.1–10 um in size
GL	10–1000 um

MLV: Multilamellar vesicle, MVV: Multivesicular vesicle, SUV: Small Unilamellar vesicles, GL: Giant liposome, LUV: Large unilamellar vesicle

Multivesicular liposome

A vesicle is composed of several non-concentric vesicles encapsulated within a single bilayer known as a multivesicular vesicle (MVV). These can be multifunctional liposome ranging in size from 2 um to 40 um.

Oligolamellar liposome

The oligolamellar liposome contains less layers of lamella compared to the multilamellar liposome. Their size ranges from 0.1 to 10 um in size.

Giant liposome (GL)

These are the largest size liposome ranging in size of 10–1000 um. This GL can be used for different diagnostic and medical purposes. They can be both SUV and LUV.[15-18]

MECHANISM OF TRANSPORTATION THROUGH LIPOSOMES

Liposome can interact with cells by four different adsorption mechanisms by specific interactions with cell-surface components, electrostatic forces, or by non-specific weak hydrophobic, which is one of the possible paths. The second possible interaction is endocytosis by phagocytic cells of the reticuloendothelial system such as macrophages and neutrophils. The third mechanism is fusion with the plasma cell membrane by insertion of the lipid bilayer of the liposome into the plasma membrane with simultaneous release of liposomal content into the cytoplasm. And the fourth mechanism is Swap of bilayer components, for instance, cholesterol, lipids, and membrane-bound molecules with components of cell membranes. It is difficult to understand what mechanism is functioning, and more than one may operate at the same time.[19-21]

ADVANTAGES

Some of the advantages of liposome are as follows:

Liposomes are biocompatible, completely biodegradable, non-toxic, flexible, and nonimmunogenic for systemic and non-systemic administrations.

Improved solubility of lipophilic and amphiphilic drugs: The hydrophobic anti-cancer drugs can be incorporated in the lipid membrane of liposome that will increase the solubility of poorly soluble anti-cancer drugs.[22]

Liposome provides selective passive targeting to tumor tissues especially cells of the mononuclear phagocytic system, for example, antimonials, amphotericin B, porphyrins, vaccines, and immunomodulators. Improved solubility of lipophilic and amphiphilic drugs.[23]

Increased potency and efficacy: Nanoliposomes can penetrate most of the biological membranes of the body. This results in higher accumulation of drug at the targeted site of action and increases the therapeutic index and efficacy of drug.[24]

Flexibility to couple with site-specific ligands to achieve active targeting: Due to adjoint of such site-specific ligands, the drug procreate its effects at the desired site only, and reduces the probabilities of drug-related toxicities.[25]

Higher Stability: Liposome by encapsulating drugs prevents the enzymatic degradation of the drug and causes more drug sustainability in the blood in the circulation.[26]

Decreased toxicity: Liposome by encapsulating drugs reduces the effective dose required for treatment and risk of dose-dependent toxicity; therefore, this improves treatment safety and efficacy and decreases side effects and adverse events occurring due to high dosage.[1]

Site avoidance effect: Liposome gets poorly accumulated in soft tissues such as kidney and heart; therefore, entrapped drugs in liposome (such as anti-inflammatory drugs, anti-cancer, and anti-infection) can have less destructive effects on the tissues. These result in a site avoidance effect of the drugs.[27]

Improved pharmacokinetic effects: Liposomes can reduce elimination of half-lives. PEG-coated liposome has longer circulation time in systemic circulation and causes slow release of drugs and reduces drug administration and increases the therapeutic index of the drug.[28]

METHODS AND PREPARATION

The development of new methods for the preparation of liposomes has been done with the aim of accessing the highest rate of loading of the soluble matter. In general, the methods of producing liposomes are divided into two categories:

(1) A method that causes physical changes in lipid bilayer and (2) methods that generate new bilayers.[29] In this research, different methods of preparation of liposomes are described based on the type of produced liposomes.

MLVs

Thin-film hydration

This method was first described by Bangham *et al.* for the preparation of MLV liposomes.[7,30] In this method, phospholipids are first dissolved in an organic solvent (dichloromethane,[31] chloroform,[32-34] ethanol,[35] and chloroform-methanol mixture).[36] The purpose is to obtain a clear lipid solution for complete mixing of lipids, then this clear lipid solution is poured into a round bottom flask and organic solvent is removed by rotary evaporation yielding. A thin and homogeneous lipid film on the sides of a round bottom flask is formed when the solvent is evaporated under vacuum at the temperature: 45–60°C. Nitrogen gas is involved to completely remove the residual solvent.[32,35,37] The final step is the dispersion or hydration of the lipid film with an aqueous media, carried out in conjunction with agitation to separate the swelling lamellae from the vessel surface and form sealed spherical structure.[38] The time for the hydration process varied from 1 h to 2 h at the temperature 60–70°C. To obtain full lipid hydration, the liposomal suspension is left overnight at 4°C.[35,39] The duration of lipid film hydration and mixing conditions is effective in determining the loading rate of the drug solution in the MLVs. The disadvantages of this method include low encapsulation, difficulty of scaling up, and the heterogeneous size distribution.[31,40]

Dehydration-rehydration method

The method of dehydration-rehydration is designed to achieve high loading rates, especially for sensitive biological molecules such as proteins and nucleic acids. In this method, first, the SUV liposomes are prepared and then converted to MLV. The SUVs are prepared by sonication method. The obtained formulation is frozen and left freeze-dried overnight. If the resulting powder is rehydrated with a small volume of distilled water, a large mlv liposome is obtained at high loading rates.[41,42]

Simple hydration of solvent–solubilize lipid

In this method, the amphiphilic dissolved in an organic solvent are hydrated in an aqueous solution without removing the organic solvent. If the used solvent is mixable with water (such as ethanol or propylene glycol), it can be removed or left at the end of the process by dialysis or filtration.[43]

Large unilamellar vesicles (LUV)

Detergent removal

This method is very important in loading and encapsulating proteins and other biological molecules used in medicine. The detergent depletion method is a mild process for the

production of a wide variety of vesicle types and highly homogeneous liposomes. The detergents at their critical micelles concentrations have been used to solubilize lipids. As the detergent is removed the micelles become progressively richer in phospholipid and finally combine to form LUVs. Used detergents include nonionic surfactants (such as n-octyl-beta-d-glucopyranose), anionic surfactants (such as two dicalcium sulfates), and cationic surfactants (such as hexadecyltrimethyl ammonium bromide). The detergents used must have a high critical concentration (C. M. C) to be easily removed.[44,45] The detergents can be removed by dialysis. A commercial device called LipoPrep (diachema AG, Switzerland), which is a version of dialysis system, is obtainable for the elimination of detergents.[46] Other techniques have been used for the removal of detergents: 1-by using Gel Chromatography involving a column of Sephadex G-25, 2-by adsorption or binding of Triton X-100 (detergent) to Bio-Beads SM-2, and 3-by binding of octyl glucoside (a detergent) to Amberlite XAD-2beads. The dialysis can be performed in dialysis bags engrossed in large detergent free buffers (equilibrium dialysis)[47,48] The advantages of detergent dialysis method are excellent reproducibility and production of liposome populations which are homogenous in size. The disadvantages of this method are that the final concentration of liposomes in the solution is low and entrapment of any hydrophobic compound is very low. The detergent also remains in the formulation. The size and homogeneity of liposomes produced using detergent depletion are based on the rate at which the detergent is removed and the initial ratio of detergent to phospholipid. The method is very time consuming and the process of removing the detergent may also remove any other small hydrophilic compound.[7,30,49]

Reverse-phase evaporation method

The reverse-phase evaporation process was first described by Szoka and Papahadjopoulos.[50] This method provided a progress in liposome technology, since it allowed for the first time the preparation of liposomes with a high aqueous space-to-lipid ratio and a capability to entrap a large percentage of the aqueous material presented. Reverse-phase evaporation is based on the creation of inverted micelles. The technique is carried out by dissolving the lipids in an organic solvent, adding a small volume of aqueous phase, then sonicating the solution to produce inverted micelles. The organic solvent is removed using a rotary evaporator and a viscous gel form then gel is mixed with a mechanical stirrer because of change the water to the water emulsion in the oil and turn it into an oil emulsion in water.[51] The advantage of this very popular preparation technique is a very high encapsulation rate up to 50% (small and large molecules such as RNA and various enzymes). A possible drawback of this efficient method is that the remaining solvent or the proof of their absence especially for using them for pharmaceutical purposes and to brief periods of sonication. The other important issue is large-scale production, which might be feasible if appropriate shear mixing devices for the creation of the microemulsion and pumps for the dilution step are available. Therefore, the process is not suitable for fragile molecules such as peptides.[38]

Double emulsion evaporation

In this method, a aqueous solution containing drug is dispersed in an organic solvent which the lipids were dissolved in it and creates the water-in-oil emulsion then both phases are homogenize by proper agitation to form the primary emulsion (W1/O). Then, the primary emulsion is emulsified with the outer aqueous phase containing appropriate stabilizer to form double emulsion (W1/O/W2). Formation of double emulsion (particulate dispersion) is followed by evaporation of the organic solvent (O) from the dispersed phase leading to a point of insolubility and consequently, hardening of the polymer encapsulating the active material. Usually, chloroform-ether mixture is used as a solvent which may be evaporated under reduced pressure through rotary evaporator or by simple stirring at ambient temperature depending on the boiling point of organic solvent.[29,52]

Solvents injection of water-miscible

This method creates single-layer and multi-layer vesicles with loading rates of 40–20%. Increased loading will depend on the formation of large single-layer buildings.

Ether injection method

A solution of lipids dissolved in diethyl ether or ether/methanol mixture is slowly injected to an aqueous solution of the material to be encapsulated at 55–65°C or under reduced pressure. The subsequent removal of ether under vacuum leads to the formation of liposomes. As a result, single-layer vesicles are produced, depending on conditions, they range from 50 to 200 nm.[40,53] The main disadvantages of the method are that population is heterogeneous and the exposure of compounds to be encapsulated to organic solvents or high temperature.[54]

Fluorocarbon injection

This method is similar to the previous one instead of the ether, Freon (CHFCL2 (Z1) is used, which is a good solvent for phospholipids and evaporates at atmospheric pressure at 9°C.[29]

Small single-layer (SUV) vesicles

Sonication

Disruption of LMV suspensions using sonic energy (sonication) typically produces SUV with diameters in the range of 15–50 nm. The sonication method is based on size transformation and involves the subsequent sonication of MLVs prepared by thin-film hydration method, using sonic energy usually under an inert atmosphere including nitrogen or argon. This method is probably the most widely used method for the preparation of SUV. There are two sonication techniques. The purpose of

sonicating is to create a uniform dispersion of small vesicles with high penetration into the tissue.[55]

Probe sonication

The probe tip sonicator delivers high energy to the lipid suspension. The possibility of overheating of the lipid suspension causes degradation. Sonication tips tend to release titanium particles into the lipid suspension, which must be removed by centrifugation before use. The bath sonicators are the most widely used instrumentation for preparation of SUV.[56,57]

Bath sonicator

The liposome dispersion in a tube is placed into a bath sonicator and sonicating for 5–10 minutes above the Tc of the lipid they are used for large volume of dilute lipids controlling the temperature of the lipid dispersion is usually easier in this method compare to sonication the dispersion directly using tip. Material being sonicated can be kept in a sterile container, unlike the probe units, or under an inert atmosphere. The lipid bilayer of the liposomes can fuse with other bilayers, thus delivering the liposome contents. By making liposomes in a solution of DNA or drug they can be delivered past lipid bilayer main drawbacks of the method are oxidation of unsaturated bonds in the fatty acid chains of phospholipids and hydrolysis to lysophospholipids and free fatty acids, as well as denaturation of thermolabile substances such as DNA and certain proteins and very low encapsulation efficiency of internal volume.[34,40,58]

High pressure extrusion method

MLVs prepared by thin-film hydration method are repeatedly passed through filters polycarbonate membranes at 20,000 psi at 4°C through a small orifice reducing the liposome size in high-pressure extrusion method. When the MLVs are pushed through the small orifice their layers are gradually separated and only one of their layers remains this method cause uniform particle size distribution by decreasing the size of the liposomes, causes uniform particle size distribution. The method is simple, rapid, reproducible, and involves gentle handling of unstable materials. The resulting liposomes are somewhat larger than sonicated SUVs. The drawbacks of the method are that the temperature is difficult to achieve and the working volumes are relatively small (about 50 mL maximum).[38]

Injection of water - miscible solvents

In this method, solutions such as ethanol, glycerin, and polyglycols are used and lipids are dissolved in the solvent and injected into water. As a result, the solvent is mixed with water, diluted and loses its solvency, meanwhile, liposomes are formed.

Ethanol injection method: The ethanol injection method was first described in 1973 by Batzri and Korn as one of the first alternatives for the preparation of SUVs without sonication. A lipid solution of ethanol is rapidly injected to a vast excess of the preheated buffer. To create SUVs, the final concentration of ethanol should not be more than 10–20 v/v%. Because SUVs are not formed at high concentrations of ethanol or after being formed their size increases rapidly.[59] The main advantage of ethanol injection method is including of non-harmful solvent as ethanol, as well as easy scale-up of the method.[40,53] The disadvantages of the method are that the population is heterogeneous (30–110 nm), liposomes are very dilute, the removal all ethanol is difficult because it forms into azeotrope with water, and the probability of the various biologically active macromolecules to inactivate in the presence of even low amounts of ethanol is high.[14]

Injection, another solvent mixable with water: In this method, solvents other than ethanol are used such as polyhydric alcohols such as glycerol, ethylene glycol, propylene glycol, and glycerol esters such as monostearate. Because these solvents are relatively harmless and if they remain soluble, they will not cause any problems.[60]

Preparation of multivesicular liposomes

The production of liposomes is by dual emulsion method. The limitation of this method is the use of volatile organic solvents.[61]

APPLICATIONS OF LIPOSOME

The aim of any DDS is to modulate the pharmacokinetics and distribution of the drug in a beneficial way. Among the variety of delivery systems, applications of liposome-based formulations and products are extremely wide, because of ability of liposomes to carry a wide variety of substances large number of drugs: Antimicrobial agents, drugs against cancer, antifungal drugs, peptide hormones, enzymes, vaccines, and genetic materials, their structural versatility and the innocuous nature of their compound.[62] Some of the main applications of liposomes in various fields are described below in Table 2:

Drug targeting

Liposomes can be incorporated with opsonins and ligands (e.g., antibodies, sugar residues, apoproteins or hormones, which are tagged on the lipid vesicles) for site-specific drug delivery system. The ligand recognizes specific receptor sites and, thus, causes the lipid vesicles to concentrate at such target sites. By this approach, the otherwise preferential distribution of liposomes into the reticuloendothelial system (liver, spleen, and bone marrow) is averted and reduces the probabilities of drug-related toxicities.[63]

Cancer therapy

Liposome-based chemotherapeutics used in the treatment of cancer such as breast cancer can improve the pharmacokinetics

Table 2: Methods for preparation of drug delivery liposomes

Drug liposome formulation	Application of liposome	Method	References
5-fluorouracil	Drug targeting	Thin-film hydration method, ethanol injection and extrusion	[86,87]
Vinblastine sulfate	Cancer therapy	Thin-film hydration method and sonication	[87]
Celecoxib	Transdermal drug delivery	Thin-film hydration method	[88]
Miltefosine	Parasitic diseases	Reverse-phase evaporation method	[89]
Tetanus toxoid	Immunology (vaccines)	Reverse-phase evaporation method	[90]
Mafenide acetate	Antibiotic therapy	Solvent evaporation and microencapsulation	[29]
Magnetite cationic (MCLs)/DNA complex	Gen delivery	Thin-film hydration method and sonication	[91]
Maghemite (γ-Fe_2O_3)	Diagnosis (MRI)	Lipid-film hydration method and extrusion	[92]
Tretinoin	Cosmetics	Thin-film hydration method	[81]
Enzymes (β-galactosidase)	Food industry	Dehydration-rehydration method	[93]
Streptomycin and chloramphenicol	Antibiotic therapy	Ether injection	[94]

MRI: Magnetic resonance imaging

and pharmacodynamics of associated drugs. Liposome can target a drug to the intended site of action in the body, thus increase its therapeutic efficacy. Anthracyclines are drugs which inhibit the growth of dividing target anti-cancer drugs to cells by intercalating into the DNA and, thus, kill mainly rapidly dividing cells. These cells are not only in tumors but are also in hair, gastrointestinal mucosa, and blood cells; therefore, this class of drug is very toxic. The encapsulation of cytotoxic agents within liposomes allows to accumulation at of anti-cancer drugs at the tumor site. In addition, the presence of the phospholipid bilayer prevents the encapsulated active form of the drug from being broken down in the body before reaching tumor tissue and also serves to minimize exposure of the drug to healthy sensitive tissue. As a result, reduces the toxicity of anti-cancer drugs.[64,65]

Transdermal drug delivery

Transdermal DDSs offer a number of potential advantages over conventional methods such as injectable and oral delivery. The main problem to the transdermal delivery system is the limitation of the penetration of macromolecules and hydrophilic drugs through the stratum corneum. The intercellular lipids of the stratum corneum perform a key role in establishing the permeability barrier of the skin. Liposome system is a suitable carrier to improve drug delivery through the skin[66,67] because they are predominantly phospholipids bilayer similar to that existence in biological membranes. Different forms of liposome preparations such as solution, creams, gels, and ointments can deliver compounds across the stratum corneum. Liposomes have high member fluidity; therefore, they can increase the permeability of skin for various entrapped drugs and deliver drugs to target. From this way and at the same time diminish the side effect of these drugs. In recent years, liposomes have been very much considered as a vesicles for transdermal drug delivery, they are regularly released from the base in topical administration, and also they tend to accumulate in the stratum corneum of the skin and after entering this layer, slowly out of it and enter the circulatory system, therefore, can act as a depot from which the entrapped compound is slowly released over time across skin. As a result, topical drugs are prepared as liposomes compared to traditional local forms, need less drug to create a therapeutic concentration in the local administration site, on the other hand, increase the duration of action and decrease the frequency of administration. As a result, side effects are reduced.[4,68,69]

Parasitic diseases and infections

Liposomes can be made in a particular size and used as a viable target for macrophages. These liposomes may be digested while in the macrophage's phagosome, thus releasing its drug. For this reason, they are suggested as an ideal carrier for treatment parasitic diseases which normally exist in the cell of MPS such as leishmania. Leishmaniasis is a group of endemic diseases caused by the leishmania intramacrophagic parasite and mainly affects the poorest populations. The main therapeutic agents against leishmaniasis are pentavalent antimonials, amphotericin B, pentamidine, paromomycin, and miltefosine, however, the use conventional chemotherapy for leishmaniasis due to high toxicity and serious adverse reactions, e.g., gastrointestinal disorders and cardiac arrhythmias, long duration of treatment and reports of drug-resistance are not appropriate. Liposomal encapsulated drugs appear as an option for the treatment of leishmaniasis, providing greater efficacy for the active and reducing its side effects by accumulate at infected macrophages and releasing drug at the desired location.[70,71]

Treatment of human immunodeficiency virus (HIV) infection

Several new drugs, such as antiretroviral nucleotide, have been developed nowadays for the treatment patients suffering of HIV infections. Liposomes can serve as vehicle for delivery of such oligonucleotides and other antiviral drugs. These potential anti-HIV nanocarriers are concentric lipid bilayers, which can be fabricated to protect molecules and to target the drugs to specific sites.[72]

Immunology

Liposomes rapidly accumulate in macrophages, so this ability can be used in vaccination and activation of macrophages. In immunology, antigens encapsulated in liposomes are developed to create antibodies, to activation passive and active immunization and for many other applications. The first application of liposomal as immunological adjuvant was reported by Allison and Gregoriadis.[73] Today, liposomes are used as immunological adjuvants in many cases such as hepatitis B-derived polypeptides, subunit antigens from the influenza virus, adenovirus type 5 hexon, allergens, and polysaccharide-protein conjugates. Liposome-based vaccines have been effective in experimental models against the viral, bacterial, parasitic infections, and even tumors. Liposome has been widely studied in adjuvant therapy include hepatitis B-derived polypeptides, subunit antigens from the influenza virus, adenovirus type 5 hexon, allergens, and polysaccharide-protein conjugates.[74]

Antibiotic therapy

Liposomes increase the effect of antibiotics for two reasons:

First, they encapsulate hydrophilic antibiotics such as vancomycin and triclosan and their lipid nature increases the entry of antibiotics into the microorganism cells. As a result, the effective dose of the drug and its toxicity decrease.

Second, they protect the entrapped drug against enzymatic degradation. For example, protect the penicillins and cephalosporins from degradation by the beta-lactamase enzyme, which is produced by certain microorganisms.[75,76]

Genetic engineering

Liposomes can connect to the target cells in various way and are, therefore, able to development the intracellular delivery of drug molecules that in their "free" form (i.e., Non-encapsulated) would not be able to enter the cellular interior due to undesirable physicochemical characteristics. This liposome property is used to transport genetic material such as DNA fragments, to specific microorganism cells with the aim of coding certain peptides.[77]

Diagnosis

Addition to the therapeutic area, liposomes are also effective in diagnosis cases such as therapeutic imaging modalities, liposomes encapsulate contrast agents and through this are employed in diagnostic X-ray, and nuclear magnetic resonance imaging.[78]

Cosmetics

In the dermatological and cosmetic field, liposomes are used because of their capability of enclosing many different biological materials and of delivering them to the epidermal cells. The moisture content of the skin has special significance in cosmetic applications, therefore Cosmetic care is concerned to equilibrate the moisture balance of the skin. Liposomes easily are hydrated and can reduce dry skin, which is on factor aging of the skin.[79] In addition, anti-inflammatory agents, immunostimulants, and enhancers of molecular and cellular detoxification within liposomes could prevent age spots, dark circles, wrinkles, and other clinical aspects of skin. According to the study, on liposomes for targeting drugs into the pilosebaceous units, has observed that liposomes are potent DDSs for treating hair follicle-associated disorders, such as acne.[80] Liposomes can increase tretinoin concentration in the epidermis and dermis and protects it from photodegradation and minimize skin irritation compared to conventional cream or gel, and this way enhance the clinical effect.[81] Briefly, the use of liposomes in nano cosmetology also has many benefits, including improved penetration and diffusion of active ingredients, selective transport of active ingredients, longer release time, greater stability of active ingredients, reduction of unwanted side effects, and high biocompatibility.

Food and farming industry

In the food industry, liposomes have been employed for developing new taste, controlling the release of flavor, improving the food color and modifying the texture of food components because they can entrap unstable compound, for example, antimicrobials, antioxidants, flavors, and bioactive elements and protect them against a range of environmental and chemical change including enzymatic chemical changes, as well as temperature and ionic strength variations and releases the ingredients at designate targets when required.[82]

In the text below, some liposomal applications in the food industry are mentioned:

Research has shown that adding proteases to the cheese mixture reduces the cost and time of the preparation of cheese As well as liposome-entrapped proteinases reduce the firmness of cheddar cheeses but increase their elasticity and improve their flavor and liposome-entrapped lipase increases cheddar cheese cohesiveness and elasticity but reduces the cheese firmness.[83,84]

In the food production industry, liposomes are used to encapsulate enzymes with the aim of stabilize the enzymes against food manufacture processes and preserving them for a long time and maintain their useful effects in foods.

Liposomes have the ability to carry and delivery proteins, enzyme galactosidase to aid the digestion of dairy foods by the lactose intolerance, vitamins (Vitamin D in cream and cheese, A and E, β_carotenes), antioxidants (α-tocopherol and glutathione), and flavors minerals such as Ca+2 and Mg+2 into foods.[85]

Future prospects

From a regulatory perspective, it is important to design a drug delivery strategy based on predefined desired attributes and to establish clinically meaningful specifications. To make a significant therapeutic impact, DDSs such as liposomes and lipid nanoparticles must serve as a drug carrier not only to improve drug stability and exposure but also to enhance the accumulation of a significant amount of drug in the target tissue. Considering future medical applications of liposomes, we can expect several novel anticancer agents, cytokines, antifungals, antibiotics, and antivirals in conventional and long-circulating liposomes. In parallel, the applications of liposomes will spread to several other areas, such as the food and nutrition industry, diagnostics, and the coating industry and cosmetic. We may soon have targeted liposome delivery systems that can potentially be used to formulate high potency drugs with significantly improved safety and efficacy.

CONCLUSION

It was concluded from the review that liposomes can be a promising carrier for improving targeted delivery of a large number of drugs: Antimicrobial agents, drugs against cancer, antifungal drugs, peptide hormones, enzymes, vaccines, and genetic materials. Liposomes are administrated orally, parenterally and topically as well as employed in a broad range of pharmaceutical and pharmacology applications with therapeutic and diagnostic purposes and as good carriers in gene delivery various drugs. Liposomal delivery systems have been approved as a suit carrier for therapeutic effectiveness in terms of duration of action and decrease in dose frequency and delivering drugs at higher efficiency and lower toxicity.

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