IJARSCT
ISSN (Online) 2581-9429
International Journal of Advanced Research in Science, Communication and Technology (IJARSCT)
Volume 3, Issue 2, March 2023
Impact Factor: 7.301

Liposomal Antibiotics for the Treatment of Infectious Diseases

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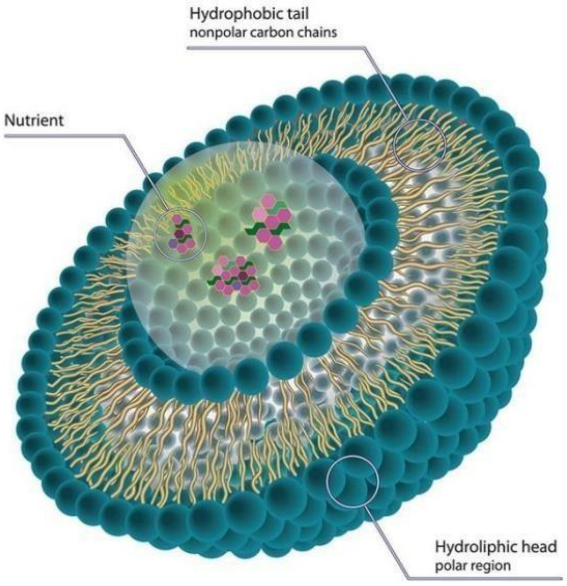
Abstract: *Liposomal delivery systems have been utilized in developing effective therapeutics against cancer and targeting microorganisms in and out of host cells and within biofilm community. The most attractive feature of liposome-based drugs are enhancing therapeutic index of the new or existing drugs while minimizing their adverse effects. This communication provides an overview on several aspects of liposomal antibiotics including the most widely used preparation techniques for encapsulating different agents and the most important characteristic parameters applied for examining shape, size and stability of the spherical vesicles. In addition, the routes of administration, liposome--cell interactions and host parameters affecting the bio distribution of liposomes are highlighted. Liposomes are safe and suitable for delivery of variety of molecules and drugs in biomedical research and medicine. They are known to improve the therapeutic index of encapsulated agents and reduce drug toxic- ity. Recent studies on liposomal formulation of chemotherapeutic and bioac- tive agents and their targeted delivery show liposomal antibiotics potential in the treatment of microbial infections.*

Keywords: Administration Routes, Infectious Diseases, Liposome Cell Interactions, Liposomes, Preparation Techniques.

I. INTRODUCTION

Infectious diseases are disorders caused by organisms such as bacteria, viruses,fungi or parasites. Many organisms live in and on our bodies. They're normally harmless or even helpful. But under certain conditions, some organisms may cause disease. Some infectious diseases can be passed from person to person.



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Antibiotics are an explicit component of antimicrobial chemotherapy implicated in the treatment of a wide variety of bacterial infections. These agents are either bacteri- cidal or bacteriostatic and exhibit synergy with other antimicrobial agents [1,2]. Resis- tance to antibiotics therapy is seen in respiratory bacterial isolates from cystic fibrosis (CF) [3] , acquired immunodeficiency syndrome (AIDS) [4] and pneumonia [5] as well as osteomyelitis [6] wounds [7] And burns [8] Resistance typically results from drug inactivation by bacterial enzymes, expression of genes involved in efflux pump system and alteration in membrane permeability to reduce intercellular accumulation of drugs [4,9,10]. Depending on the route of administration, drugs must pass through dif- ferent tissues before reaching the infection site. Systemic drug delivery puts drugs at the risk of inactivation and may cause intoxication. To compensate for the loss, high concentrations and long period of administration of antibiotics are prescribed, which makes the matter worse.[2] Furthermore, the ability of some bacteria to survive inside the phagocytic cells prevents access of the antimicrobial agents to eradicate the infection and, transition of planktonic bacteria to biofilm community increases bacte- rial resistance to antibiotics [11, 13] To overcome these problems, drugs are adminis- tered in carrier systems such as micelles [14] , dendrimers [15] and liposomes [16] Because liposomal membrane mimics cell membrane, research into improving lipo- somal formulations utility as a drug delivery system attracted scientists and pharma-ceutical industry alike [17, 18] Most recently, liposomes have been commonly used in cosmetic [19] food [20] agricultural [21] and pharmaceutical industries for delivery of biomolecules such as drugs, genetic materials and pesticides. Liposomes are spherical lipid vesicles ranging from nano- meters to micrometers in size. They consist of one or more lipid bilayers surrounding an aqueous core. Liposomes are a relatively safe delivery system because they are biocompatible and biodegradable [22]. There are several rationale purposes for using liposomes as carriers for biologically active com- pounds. Currently, liposomes are designed to demolish or reduce toxicity of the entrapped biologically active agents, to direct targeting active agents to a desired delivery site, to pro- tect the drug from unwanted metabolic breakdown, to improve the pharmacokinetics of the active agents and to increase their accumulation at the target site [23-25]. They are usually classified into three categories (Figure 1): small unilamellar vesicles (SUVs) or oligolamellar vesicles (OLVs), large unilamellar vesicles (LUVs) and multilamellar vesicles (MLVs) depending on the number of bilayers present in the vesicle and by their size [26] Regarding the variety of liposomal applications, the physi- cochemical properties of liposomes can be modified by chang- ing i) the net surface charge; ii) pH sensitivity; iii) heat sensitivity or iv) proportions and type of lipids in the formu- lation Liposomes' ability to encapsulate not only hydrophilic agents, but also lipophilic ones has proven to be a highly valuable characteristic [27]. Increased bacterial drug resistance to common therapies and ability of some species to form drug-impermeable capsules and biofilms imperme- able to antibiotics have become a main problem in modern medicine [28] Liposomes can introduce components with poor penetration such as antibiotics into bacterial cells such as Pseudomonas aeruginosa [29] Intensive researches are now focused on liposome-encapsulated antibiotics to enhance their pharmacokinetic properties and bactericidal activities as well as reducing the drugs' adverse effects [27,30] Due to liposomes complex physicochemical properties, there are many factors toconsider when preparing a liposomal formulation. For exam- ple, different lipid compositions that constitute the liposome as well as its size and surface charge which affect the encapsu- lation efficiency (EE) along with releasing rate of the antibiotic ics. While many investigators are making efforts to discover new antibiotics, others are focused on enhancing the efficacy of currently available antibiotics in the form of liposomal formulations [31,33].

II. LIPOSOMES AS A DRUG DELIVERY SYSTEM

Liposomes have been successfully used in the delivery of anti-Cancer, antibacterial and antifungal drugs in vitro and in vivo Developing liposomal formulations holds great interest in Biomedical research because they may serve as a sustained Drug release system [34], which results in prolonged half-Life of the active agents. The extended half-life provided by Liposomal formulation may lead to a decrease in frequency And length of drug administration [35,36] Different methods of preparation and characterization, as well as the stability And interaction of liposomes with cells, are discussed in this brief.

III. METHODS OF PREPARATION

There are a wide variety of liposomal preparation methods That fall into two main categories of conventional or mechan-Ical methods. Conventional methods include the dehydra-Tion— rehydration vesicle, reverse phase

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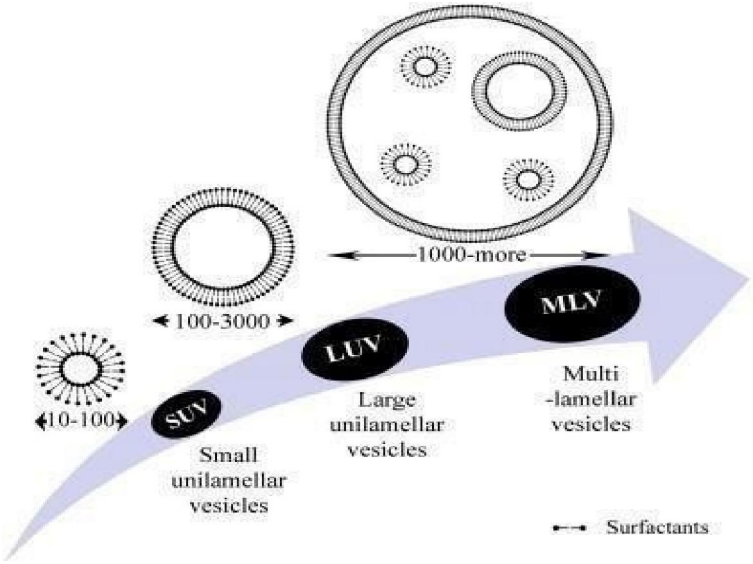
evaporation, injection And detergent removal methods which involve the dissolution O lipids in an organic phase followed by the addition of an Aqueous solution. The mechanical methods, on the other Hand, involve a mechanical force that results in a homogeneous Mixture of liposomes.

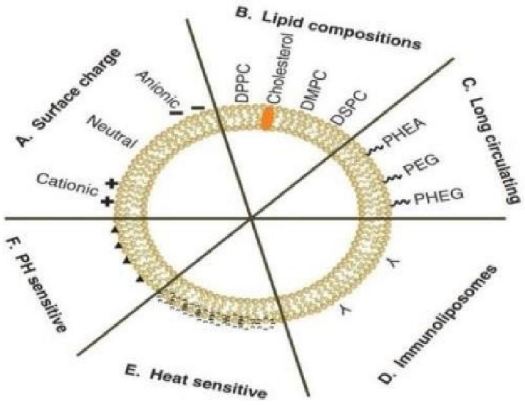


4.3 Conventional Methods

A. DEHYDRATION—REHYDRATION

The dehydration—rehydration vesicles (DRV) method is the Simplest and most widely used procedure for liposome prepa-Ration[31,33]. The process of preparing DRV involves the dis-Solving of lipids in organic solvents such as chloroform or a Chloroform/methanol mixture in a round bottom flask, fol-Lowed by evaporating the organic phase to form a thin layer of lipid film. The last step of preparation involves rehydration of the lipid film with an aqueous phase. When the dry lipid Films are rehydrated, lipid lamellae are formed, mechanical Agitation such as shaking or vertexing may apply to detach Lipid film from the flask [37]. The DRV technique has been Employed by several laboratories. Liposomal formulation Prepared by Halwani [38] Encapsulated amikacin in Liposomes consisted of distearoyl glycerophosphocholine (DSPC) and cholesterol in molar ratio of 2:1 with an entrapped Percentage of 52.08 %. Another study investigated the encapsulation of ciprofloxacin in two cationic liposomal formula-Tions that consisted of phosphatidylcholine (PC), cholesterol And dioleoyl trimethylammonium propane (DOTAP) in molar

Classification of liposomes by size - Multilamellar vesicles (MLVs), large unilamellar vesicles (LUVs) and small Unilamellar vesicles (SUVs). Modification of the physicochemical properties of Liposomes. (A)
Neutral or charged, (B) lipid compositions, (C) Long circulating, (D) immunoliposomes, € heat sensitive And (F) pH sensitive.



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B. Reverse Phase Evaporation

Reverse phase evaporation vesicle (REV) is a procedure for Liposome preparation with a large internal aqueous space. Preparation of liposomes using this method results in large Unilamellar and oligolamellar vesicles that are able to entrap large macromolecules with high EE . The procedure is based on two steps: adding an aqueous phase to format a phospholipid monolayer surrounded by water and then add- ing an excessive organic solvent. The lipid mixture is trans- ferred into a round bottom flask and dissolved with solvent, followed by removing the solvent under reduced pressure by rotary evaporator and then flush- drying with nitrogen gas. The solvents that have been successfully used are diethyl ether, isopropyl ether, halothane and trifluorotri- chloroethane. Lipids are then redissolved in the organic phase, followed by adding aqueous solution of the bioactive agent. The solution is then sonicated to produce inverted micelles. The organic solvent is removed and a viscous, gel-like matrix forms. As the majority of solvent has been removed, the gel collapses and an aqueous suspension of vesicles forms. There are drawbacks of REV when a drug encapsulated into the vesicles is in contact with the organic phase and the exposure to mechanical agitation Ciprofloxacin-loaded liposomes with different compositions and surface charge have been pre- pared by REV. Positively charged liposomes exhibited the highest EE (82.01%). The maximum amount of ciprofloxacin entrapped was achieved in liposomes prepared from soya PC, cholesterol and stearylamine in a molar ratio of 5:3:1. Nicolosi et al. reported the successful encapsulation of vancomycin into liposomes consisted of dioleoyl phosphatidyl ethanolamine, dipalmitoyl phosphatidylcholine and choles- terol hemisuccinate in molar ratio of 4:2:4 using REV method. The liposomal vancomycin exhibited an entrapment efficiency of 65%.

C. Injection Method

The ethanol/ether injection method involves dissolving lipids In ethanol or ether, then slowly injecting this lipid solution Through a fine needle into the aqueous phase, followed by Evaporating the organic solvent. The injection results in the Formation of unilamellar liposomes with a high EE [39]. Com-Paring the ethanol injection with the ether injection method, The latter is more advantageous since residual ethanol might be a concern; whereas ether is immiscible with aqueous solutions and can be heated to remove the solvent under vacuum Chorachoo et al. prepared rhodomyrtone liposomal formulations that consisted of PC and cholesterol with ratio of 4:1 by ethanol injection method. The encapsula- tion efficiencies of liposomal formulations ranged between 51 and 65%. The highest percentage of rhodomyrtone entrapped was in liposomes of 60 µmol/ml of total lipid con- centration. The liposomal rhodomyrtone exhibited higher activity compared with the free formulation against Staphylo- coccus aureus. Another study investigated the encapsulation of amphotericin B into three liposomal formulations prepared by ethanol injection method and consisted of soya PC and cholesterol, dimyristoyl phosphatidylcholine and cholesterol or hydrogenated soya PC and cholesterol in molar ratio of 7:3The EE of amphotericin B ranged between 93 and 97%. 2.1.1.4 Detergent removal method The detergent is used to solubilize the lipids in micellar solution . The detergent protects the hydrophobic part of lipids from interacting with the aqueous solution; thereby micelles are formed instead of liposomal vesicles. After drying the lipids mixture,an aqueous phase that contains hydrophilic drugs is added to prepare detergent-- lipid micelles. Liposomes are spontaneously formed once the detergent is removed by dialysis, column chromatography or adsorption. One of the drawbacks of liposomes formation by this technique is the use of detergent removal procedures, which are time consuming and might result in removing other hydrophilic componentsAs well, only few detergents are appropriate with this method such as alkylglycosides, sodium cholate and alkyloxypolyethylenes. Using this method, Daemen et al. . showed that 98% of the doxorubicin was encapsulated within liposomal vesicles consisted of PC, cholesterol and phosphatidylserine in molar ratio of 4:5:1.

3.2 Mechanical Methods

A mechanical force is applied to alter the size, lamellarity or homogeneity to produce a liposomal population with a specific size or property. The methods applied most often after lipo- some preparations are sonication and extrusion. These methods result in size, lamellarity and heterogeneity reduction.

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A. Sonication

Sonication is a simple method for liposome size reduction that can be achieved by exposing the MLVs to ultrasonic irra- diation. Two sonication techniques can be used: i) probe son- ication or ii) bath sonication. The probe sonicator delivers high energy to the lipid, but has the disadvantage of degra- dation caused by overheating the lipid suspension . The probe sonicator also tends to release titanium particles that need to be removed from lipid suspension [40]. Bath sonicator, however, enables controlling the energy that is delivered to lipid, thereby it prevents lipid overheating and enhances the reduction of liposomal size. Bath sonication also is the most widely used technique for large volume preparations. Mugabe et al. successfully prepared liposomal formula- tions that loaded different antibiotics including gentamicin, tobramycin, amikacin and erythromycin by DRV. After homogenization was performed via sonication, the resultant liposomal formulations had average sizes that ranged from 163 to 260 nm.

B. Extrusion

In this method, the size is reduced when the liposomes are forced to pass through polycarbonate filters with pore sizes of 1 µm under moderate pressures, followed by several cycles of extrusions through filters of decreasing pore size ranging from 0.6 to 0.1 µm at elevated temperatures . There are disadvantages with the extrusion method, including the long period of time required to reduce the size and the high prod- uct losses that may occur due to clogging of the extrusion membrane. Liposomal polymyxin B of defined size and homogeneity was prepared by sequential extrusion of the multilamellar vesicle through a double stacked polycarbonate membrane. The resultant liposomes had a mean diameter of 172 nm. Another study also improved homogeneity and reduction in size when liposome-loaded vancomycin was extruded. The average size of liposomal vesicles was 103 nm.

C. Micro Fluidization Method

Micro fluidization is a technique for reducing liposomal size, which is used in the pharmaceutical industry for large-scale production . The method is based on splitting a fluid stream into two parts and passing them through a fine orifice under high pressure (10,000 psi) to guide the flow inside the interaction chamber . The high pressure then directs the flow stream through micro channels toward the impingement area. Inside the interaction chamber, cavitation, along with shear and impact, reduces liposome size . However, a disadvantage of the micro fluidization method is the high pressure required to reduce the size, which may result in partial degradation of the lipids. As per the authors' knowledge, this method has not been widely applied in pre- paring liposomes for treating infectious diseases, however, Boltic et al. . reported the suitability of micro fluidization method to reduce the size of liposome-loaded antibiotics. The mean diameter of the liposomal vesicles after five homogenizing cycle was found to be 380 nm.

3.3 Methods of Characterization

Lirepared by any methods must be characterized. The most important characteristic parameters to be deter-Mined for optimizing stability and shelf life of liposomal Formulations are particle size, lamellarity, zeta potential And EE.

A. Particle Size

Size and size distribution measurements of liposome formula- tions are important characteristic parameters that indicate the homogeneity of liposomes. Lack of change in the average size and size distribution can be used as indicators of long- term stability. Dynamic light scattering (DLS), electron microscopy and gel exclusion chromatography are widely used to measure the size of liposomes. The basic principle of DLS is a measure- ment of the diffusion coefficient as a result of Brownian motion. The diffusion coefficient is then used to calculate the size of the liposome. Transmission electron micros- copy (TEM) at cryogenic temperature and freeze-fracture TEM are also used to determine polydispersity and size. However, light scattering and electron microscopy have their own advantages and drawbacks[40]. For instance, light scatter- ing provides the particle size of the entire sample, but it does not determine the morphology of liposomes. Additionally, this technique measures aggregation of two or more liposomal spheres as one vesicle which is larger than the actual size of a single liposomal sphere. Electron microscopy can determine the shape and actual size of particles; however, only a small population can be measured. A simple but powerful method is gel exclusion chromatography, in which a correctly hydro- dynamic radius can be detected. The main drawback of this

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method is the positively charged colloidal particles in columns that tend to clog due to the possibility of electrostatic interactions with the medium which may have a negative charge.

B. Lamellarity

The lamellarity of liposomes can be determined by measuring the phosphorus nuclear magnetic resonance (31P-NMR) sig- nal of the phospholipid head groups of liposomes before and after the addition of manganese ions (Mn2+) as a para- magnetic agent. The Mn2+ interacts with the negative charge on phospholipids of the outer liposomal surface. The interac- tion results in broadening and reduction of the resonance sig- nal. Direct comparison of the height peak of the two signals reveals the ratio of the amount of outer to inner phospholi- pids. Although this method is commonly used, parameters including buffer and Mn2+ concentrations as well as pH may affect the method accuracy. Microscopic techniques including scanning electron microscopy (SEM), confocal laser scanning microscopy (CLSM) and cryo-TEM are also used to determine the lamellarity. Not only do these show the accurate lamellarity, they also give additional information such as shape and size. The size and lamellarity can be provided as well by small-angle X-ray scattering (SAXS).

C. Zeta Potential

The potential indicates the overall charge present on the colloidal systems. The zeta potential measurement can also indicate stability of colloidal systems. Positive or negative Surface charges on liposomes indicate higher stability due to surface repulsion between similarly charged particles, hence inhibiting the aggregation of liposomes. Measuring the zeta potential is also important for controlling the fusion and precipitation of liposomes, which affect liposomal stability.

D. Encapsulation Efficiency

EE is indicative of the quantity of drugs entrapped in lipo- somal formulations. It is important as EE can be used to opti- mize the formulation composition before studying the behavior of these entrapped agents in physical or biological systems. For water-soluble drugs, encapsulation means the entrapment within the aqueous core. For lipophilic drugs, it means entrapment within lipid bilayers. After removal of non-entrapped drugs from the aqueous phase, total lysis of liposome vesicles can be induced by addition of a detergent such as Triton X100 in an effort to measure EE. EE is usually defined as the percent fraction of entrapped drug to that of the initial concentration used in the liposomal preparation . High performance liquid chromatography (HPLC) is com- monly used for determination of EE. Spectrophotometry, fluorescence spectroscopy, enzyme- based methods, microbio- logical assays and electrochemical techniques are also used for determining the EE depending on the nature of the entrapped materials.

3.4 Stability of Liposomes

Stability of liposomes involves physical and chemical stability. In the pharmaceutical industry and in drug delivery, the capa- bility of the product formulation to remain stable within a defined period of time is very important. The physical instability can be indicated by the increase of liposome size as well as the ratio of lipid to entrapped agent due to fusion and aggregation of membrane bilayers or leakage of encapsulated materials. Physical stability can be improved by storage of liposomes at low temperatures. Geusens et al. Studied the stability of cationic liposomes for 28 days at 4 and 25C and found that the particle size was stable at 4C but increased from 100 to 160 nm at 25C. Chemical instability can occur by hydrolysis or oxidation of lipids.

Hydrolysis removes hydrophobic chain of ester bonds, thereby leading to lipid destruction and leakage of encap- sulated materials. Unsaturated lipids are more likely to be prone to oxidation from reactive oxygen species, thereby affecting liposomal fluidity. However, chemical and phys- ical stability of liposomes can be enhanced by lyophilization process which has been found to be suitable for long-term stability.

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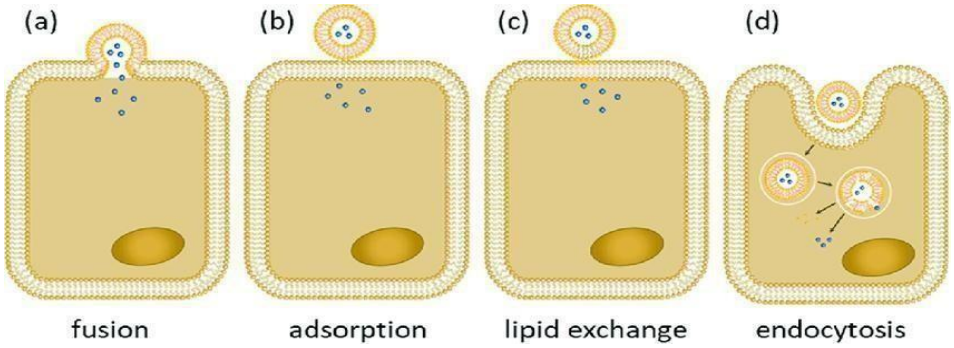
3.5 Interaction of Liposomes with Cells

Interest in liposomes is based on their biological membrane- like structure consisting of lipids organized in bilayer confi- guration. The device prevents its content from being released rapidly and, on their ability to interact with host cells in several fashions including lipid exchange, adsorption, endocytosis or fusion



Schematic representation of possible mechanisms of liposome cell interaction. (A) Fusion, (B) adsorption, (C) lipid Exchange and (D) endocytosis.

A. **LIPID EXCHANGE**

Lipophilic materials can be transferred from liposomes to the cell membrane by lipid exchange. Lipid exchange is a pro- posed method where liposomes exchange their lipids for the lipids of diverse cell membranes Although the exact mechanism is not fully understood, one possibility is the transfer of lipid monomers mediated by lipid exchange pro- teins existing at the cell surface. It is also possible that the outer monolayer of vesicles and the cell membrane undergo reversible transient merger. Finally, an enzymatic exchange of acyl chain may take place between the liposomes and plasma membrane lipids of the host cells. 2.4.2 Adsorption Adsorption of liposomes to the cell membrane is another mechanism of liposome—cell interaction. Adsorption occurs without merging of liposomes with cell membrane. When attractive forces such as electrodynamic interactions, van der Waals, hydrophopic insertion and hydrogen bonding exceed the repulsive forces such as electrostatic interactions, steric, hydration and protrusion, adsorption of liposomes into the cell membrane proceeds. 2.4.3 Endocytosis Cells with phagocytic activity engulf liposomes into endo- somes. The endosomes fuse with the lysosomes resulting in the formation of phagosomes. Lysosomal enzymes digest the lipids in the phagosomes and convert them to fatty acids. Lip- osomes' content is then released intracellularly

B. FUSION

Fusion of biological membranes is a crucial process in the intracellular delivery of lipids. Close contact of liposomes leads to intermixing and diffusion of liposomal lipids with the lipids of the target plasma membrane, thereby allowing entrapped agents in the aqueous compartment to be injected directly into the cytoplasm. On the other hand, incorpo- rated agents in the lipid bilayer are delivered into the bilayer membrane of the cell.

IV. ROUTE OF ADMINISTRATION

Encapsulated agents in liposomes might be introduced into a biological system by different anatomical routes. Delivering medication to a biological system may proceed via oral, intravenous or pulmonary routes.

4.1 Oral Administration

This route is the preferred means of delivering medication due to the safety, ease of administration and its widespread acceptance by patients. Oral administration of lipid-based encapsulation systems has a direct impact on drug perfor- mance in vivo. Lipophilic drugs may dissolve in water very poorly, but in gastrointestinal fluids they are often solubilized by bile to a significant extent. Thus, orally administered lipo- somes that have a large surface area enable pancreatic lipase to efficiently hydrolyze triglycerides, promoting solubilization of the lipophilic drug in the aqueous environment of the intesti- nal lumen. Gershkovich et al. Examined the pharma- cokinetics of liposome-loaded amphotericin B administered orally and found that the oral liposome formulation has the potential for improving therapeutic treatment and prophylaxis of systemic fungal infections.

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4.2 Intravenous Administration

Intravenous administration is the infusion of water-soluble materials directly into a vein. As systemic circulation supplies blood to the whole organism, liposomes are transported from the site of injection directly to the heart via the venous net- work and then to organs. On administration of liposomes to systemic circulation, however, liposomes are cleared rather quickly from the blood by the mononuclear phagocytic sys- tem (MPS) . Thus, diverse strategies have been developed to extend the drugs' half-life in circulation. For example, incorporation of certain glycolipids such as phosphatidyl ino- sitol in the bilayer resulted in shortened clearance time and reduced uptake by the MPS in the spleen and the liver. Conjugating a stealth component such as polyethylene glycol (PEG) on the liposome surface resulted in prolonged cir- culation . The pharmacokinetics of intravenously adminis- tered conventional liposome-loaded gentamicin showed that plasma half-life was prolonged compared with the free drug .

4.3 Pulmonary Drug Delivery Liposome

Encapsulated active agents can be delivered directly to the lung for local treatment of pulmonary diseases. This route offers greater access of active agents to the target site and allows for the use of effective but lower drug doses with reduced systemic toxicity. Liposomes seem to be a suitable and attractive option for therapeutic agent delivery to the lung, since they can be prepared from components compatible to the lung. Liposomal formulations have been deliv- ered to the lung in the form of an aerosol, which can deliver the drug particles by inhalation either through nebulization as droplets or dry powder inhalation.

A. Nebulization

Nebulization is a method of delivering active agents dissolved in liquid in the form of a fine mist inhaled into the lung by using nebulizing devices. These fall into two categories: either ultrasonic or jet flow devices . Nebulization is dependent on physiochemical properties of the drug that can be categorized as a soluble drug in solution (e.g., water, saline or cyclosporine in alcohol) or an insoluble drug suspended in liquid. Ultrasonic devices have the advantage of delivering medication in a short time, but they are not widely applicable with macromolecules due to denaturation of recombinant human deoxyribonuclease (e.g., dornase a) by overheating. Thus, ultrasonic devices are limited in their therapeutic use. Jet flow devices can be applied in order to deliver var- ious types and volumes of drug solutions in higher concentra- tions. For example, Weers et al. investigated the inhalation of liposome-loaded amikacin in terms of pulmonary deposi- tion, clearance and safety. Inhalation of liposome-loaded ami- kacin was well tolerated up to 120 mg

B. Dry Powder Inhalation

Dry powder inhalation is an alternative methodology for aero- solization and delivery of medication to the lung in the form of a dry powder. Dry powder inhalers (DPIs) are an alterna- tive technique to pressurized metered dose inhalers (pMDI) for delivering active agents. DPIs provide the advantages of increased efficacy with simplified and shortened time of drug administration. A case in point is budesonide, a corticosteroid that inhibits inflammatory symptoms like edema seen in chronic obstruc- tion pulmonary disease (COPD). Liposome- encapsulated budesonide for DPIs has been found to provide a sustained release for longer periods of time while reducing systemic toxicity.

V. BIO DISTRIBUTION

The use of liposomes in drug delivery can alter the biodistri- bution and the rate of clearance of the drug by causing it to adopt the pharmacokinetic parameters of the liposomes. After intravenous administration, liposomes are rapidly cleared from the systemic circulation, since they are recognized as for- eign bodies by MPS of the reticuloendothelial system (RES), particularly Kupffer cells in the liver and spleen . The increased rate of MPS uptake is due to opsonization by serum proteins such as albumin, lipoproteins, immunoglobulins and the complement C3a and C5a fragments [41]. Numerous stud- ies have focused on investigating the factors responsible for the regulation of this interaction. The uptake rate of MPS is affected by liposome properties such as size, surface charge, membrane lipid packing and fluidity. The circulation kinetics of liposomes sized at 360, 230 and 120 nm showed that liposomes with a mean size of 120 nm exhibit a slower removal rate from the blood compared with 230 and 360 nm . The use of charged lipids in liposomes has a direct effect on liposome pharmacokinetics as well. Pre- vious studies have shown that the presence of negatively

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and positively charged lipids in liposomes resulted in a high uptake rate of liposomes by RES . Furthermore, interactions of liposomes with serum proteins including apolipopro- tein are highly dependent on lipid composition. It is generally accepted that the effect of bilayer fluidity and manipulation of lipid composition can have an impact on liposome clearance from circulation. For instance, absence of cholesterol from liposomes resulted in bilayer destabilization by high-density lipoproteins, thus quickly eliminating liposome compo- nents from systemic circulation. Different strategies have been developed to overcome the rapid liposomal systemic clearance by coating the surface of liposomes with immobile molecules. The basic principle of these inert molecules is that a hydrophilic polymer such as glycolipid or poly amino acids, exhibiting a flexible chain that forms a periliposomal layer. This periliposomal layer hindered binding of blood plasma protein to liposomes, thereby interaction of MPS with liposomes are inhibited. Methods of extending liposome blood circulation times are: grafting of PEG, poly (hydroxyethyl-L-asparagine) (PHEA) and poly(hydroxyethyl- L- glutamine) (PHEG).

VI. TARGETING OF LIPOSOMES

The delivery of liposomes to a specific site involves shuttling it to the target area while reducing its exposure to normal tissues. Liposomes have been employed for accomplishing the delivery of therapeutic agents to a selected site by two mechanisms, known as passive and active targeting.

6.1 Passive Targeting

Passive targeting for liposome delivery uses the natural tendency of certain cells upon injection into the circulatory system. For example, liposomes can be taken up by RES in a passive manner. This uptake can be very useful in targeting diseases associated with parasites living inside macrophages such as leishmaniasis, candidiasis and listeria. Once the lipo- somes are engulfed by the macrophages, the macrophages will degrade the liposomes resulting in the release of encapsu- lated drug within the macrophage. Therefore, the drug will reach the target site directly. Another example is that liposomes with a relatively small diameter can extravasate and accumulate in tissues characterized by leaky vasculature, such as solid tumors. This accumulation which occurs due to retention of liposomes at sites of enhanced vascular permeability will result in the creation of a high local drug concentration.

6.2 Active Targeting

Active targeting of liposomes can be applied to target-specific tissues or cells through controlling the movement of liposomal vesicles by coupling specific ligands into the liposomal structure to direct the vesicles. The so-called immunolipo- somes improve the therapeutic availability of encapsulated drugs and minimize the adverse effects to non-target cells within pathological tissues. Samples of active targeting liposomal structure include concanavalin A-modified lipo- somes, mannose-modified liposomes, monoclonal antibody (mAb)- modified liposomes, folate-modified liposomes and transferrin-modified liposomes.

A. Concanavalin A-Modified Liposomes

Lections are glycoproteins or proteins receptors that recognize sugar molecules, thereby capable of binding to glycosylated molecules on cell membrane . The immobilization of carbohydrate ligands onto liposomal surface have led to the development of targeted liposomal delivery system based on carbohydrate— lectin interaction. Sudheesh et al. . Reported that a concanavalin A- anchored liposomal ampho- tericin B exhibited higher activity on inhibiting Candida albicans growth within biofilm community compared with conventional liposomes loaded with amphotericin B

B. Mannose-Modified Liposomes

Another approach to target liposomes in infectious diseases is grafting mannose, instead of lectin, on liposomal surface. Man- nose has the ability to recognize mannose receptors including mannose-binding lectins, which are highly expressed in cells of immune system such as macrophages and dendritic cells. In addition, mannose-binding proteins are capable of binding to a wide variety of cellular components including lipopolysac- charides, lipoarabinomannan and lipophosphoglycan . Chono et al. reported a higher efficacy for mannosylated liposomal ciprofloxacin against bacteria compared with unmodified liposomal ciprofloxacin in vitro. Same study showed that targeting ciprofloxacin to alveolar

IJARSCT
ISSN (Online) 2581-9429
International Journal of Advanced Research in Science, Communication and Technology (IJARSCT)
Volume 3, Issue 2, March 2023
Impact Factor: 7.301

macrophages in a rat model of pulmonary infection was significantly higher in mannosylated liposomal ciprofloxacin than conventional liposome-loaded ciprofloxacin.

C. Monoclonal Antibody-Modified Lliposome

Antibodies are frequently used ligands because they can be applied against a variety of antigens and often exhibit high affinity and selectivity for their antigen. A tumor-specific mAb 2C5 is capable of recognizing a wide variety of tumor cells. This antibody was used to modify the surface of liposome-loaded meso- tetraphenylporphine (TPP) for tumor photodynamic therapy in vivo. The modification of liposome-entrapped TPP by mAb 2C5 resulted in enhancing the efficacy of TPP and increasing the accumulation of the drug in tumor cells. However, it has been reported that using whole antibodies may trigger complement-mediated cytotoxicity and antibody-dependent cellular toxicity. To prevent these effects, Fab fragments can be used instead of using the whole antibody. Modifying liposomes with antibody fragments resulted in prolonging the circulation time and enhancing the accumulation of liposomes in solid tumors.

D. Folate-Modified Liposomes

Since folate receptors are often overexpressed in tumor cells, targeting these cells with folate-modified liposomes has been successfully applied. Indeed, intravenously administered folate-targeted liposome-loaded doxorubicin in mice bearing KB tumors was investigated. Surface modification of liposome- loaded doxorubicin with folate increased the accu- mulation of drug in tumor tissues and antitumor efficacy of the doxorubicin while prolonging the circulation time.

E. Transferrin-Modified Liposomes

In addition to antibody- and folate-targeting liposomes for tumor cells, modifying the liposomal surface with transferrin has also attracted attention. Transferrin receptors are overex- pressed on the surface of a variety of tumor cells and can be internalized after binding of transferrin to cell receptors Therefore, the coupling of transferrin into the liposome struc- ture offers longevity and the ability for drug delivery into the tumor. Transferrin-PEG-liposome-loaded oxaliplatin injected intravenously into colon tumor-bearing mice was investigated and found that surface modification of liposomal formulation exhibited a long circulation time and low uptake rate by RES in vivo as well as enhanced accumulation in tumor cells for over 72 h after administration and suppressed tumor growth

VII. TOXICITY OF LIPOSOMES

Liposomes are usually considered as biocompatible, biode- gradable and relatively non-toxic because they are composed of lipids from natural sources that reduce the toxicity of entrapped bioactive agents. Previous studies showed that lipo- somes prepared from naturally occurring compounds are not toxic to culture cells in vitro . However, when toxicity is associated with empty liposomes, it has not resulted from the lipids; rather, toxicity is coupled with the liposomal net charge and presence of volatile organic solvents. A previous study has reported that charged liposomes show highly cytotoxic effects whereas neutral liposomes are not toxic. Preparation of liposomes using positively charged lipids exhibited a highly toxic effect to epithelial lung cells; whereas negatively charged liposomes were relatively not toxic . Another study investigated the effect of charged liposomes on the buccal cells and found that positively charged lipo- somes were toxic; whereas negatively charged liposomes exhibited relatively low toxicity. The cytotoxicity of charged liposomes has not been completely elucidated. How- ever, it has been proposed that the cytotoxicity resulted from the intermixing of cationic lipids in liposomes with the anionic lipids of cell organelles such as cardiolipin in the mitochondrial membrane. Another study investigated cationic liposome toxicity in the lungs and showed that posi- tively charged liposomes can induce toxic reactive oxygen intermediates. Although cationic liposomes are toxic, they play an important role as vaccine delivery systems. The majority of liposomal preparation methods require the use of organic solvents or detergents to solubilize the lipids. Residues of these solvents might not be removed completely from the final liposome solution, causing a high potential for cytotoxicity via multiple suggested mechanisms. These mechanisms could include enzyme inhibition, protein dena- turation and cell membrane modification as well as extraction of outer cellular components such as lipids, cholesterol and proteins

IJARSCT
ISSN (Online) 2581-9429
International Journal of Advanced Research in Science, Communication and Technology (IJARSCT)
Volume 3, Issue 2, March 2023
Impact Factor: 7.301

VIII. APPLICATION OF LIPOSOMES

8.1 In Vitro Studies

Although polymyxin B can control variety of bacterial infec- tions including P. aeruginosa, its toxic side effects, including ototoxicity, nephrotoxicity and neuromuscular blockade are barriers to its use. However, it has been shown that the application of liposomal formulations could attenuate the side effects of drugs. Furthermore, in vitro studies on Bor- detella bronchiseptica, P. aeruginosa, Escherichia coli, Klebsiella pneumoniae, Acinetobacter lwofii and Acinetobacter baumannii strains showed that encapsulation of polymyxin B in lipo- somes improved antimicrobial activity and reduced bacterial population in the presence of polyanions and sputum, thereby liposomes protect polycationic antibiotics from inactivation by polyanionic components present in sputum. Liposomal formulations consist of dicetyl phosphate (DCP) or dimyristoyl phosphatidyl glycerol (DMPG) loaded with vancomycin were evaluated in vitro against methicillin- resistant Staphylococcus aureus (MRSA) . Both liposomal formulations showed improvement in the antimicrobial activity of vancomycin. Minimum inhibitory concentrations (MIC) of the liposomal formulations against MRSA strains were two- to fourfold lower than that of free vancomycin. Likewise, the minimum bactericidal concentrations (MBC) of both liposomal vancomycin were fourfold less as well. Incorporation of vancomycin or ciprofloxacin in cationic, anionic and neutral liposomes improved the efficacy of encap- sulated drugs against S. aureus. Cationic liposomes, however, showed more potent activity than neutral and anionic formu- lations. Another study demonstrated that cationic liposome-loaded ciprofloxacin showed two- to four-times higher antibacterial activity compared with free drug against Gram-negative bacteria including P. aeruginosa, E. coli and K. pneumoniae. The enhanced activity of cationic formula- tion might be explained by the interaction of negatively charged bacterial cell membrane with positively charged liposomes surface. This interaction led to increased accu- mulation of encapsulated drugs in the periplasm, allowing a large number of antimicrobial molecules to diffuse in the cytoplasm. Aminoglycosides including amikacin, netilmicin and tobra- mycin loaded into cationic liposomes composed of lecithin, stearylamine and cholesterol or anionic liposomes consisted of lecithin, DCP and cholesterol, were investigated in vitro. The liposomal formulations exhibited a stabled release pro- file in human pooled sera, however, there was no significant difference in antibacterial activity between encapsulated and free drugs. Absence of enhanced activity of liposomes-encapsulated amikacin, netilmicin and tobramycin was explained in another study by the slow release of the drugs from liposomes, which prevented a sufficient amount of anti- biotic to act directly on bacteria. However, other studies reported that liposomal aminoglycosides fuse with the outer membrane of P. aeruginosa and Burkholderia cenocepacia lead- ing to the delivery of a high dosage of aminoglycosides into bacterial cells as confirmed by TEM, immunocytochemistry, lipid mixing assays and flow cytometry. Thus, liposomes suppress the drug resistance of infectious organisms by offering a protection for antimicrobial agents from being efflux. Encapsulation of amikacin, tobramycin and genta- micin in liposomes consisting of dipalmitoyl glycerophospho- choline (DPPC) and cholesterol (in molar ratio of 2:1) exhibited more potent anti-pseudomonal activity than the free drug. The liposome- encapsulated aminoglycoside formulations also improved killing time and prolonged anti- microbial activity. Furthermore, a 64-fold reduction with ami- kacin (512 mg/l for free drug vs 8 mg/l for liposomal amikacin), a 128-fold reduction with tobramycin (1024 mg/l for free tobramycin vs 8 mg/l for liposomal tobramycin) and a 16-fold reduction with gentamicin (256 mg/l for free drug vs 8 mg/l for liposomes) was observed. Similar results for liposomes-loaded gentamicin in the MIC reduction were noted for liposomes consisting of dimyristoyl glycerol phospho- choline (DMPC) and cholesterol (in molar ratio of 2:1) [124]. Furthermore, co-encapsulation of bismuth ethandithiol (BiEDT) with tobramycin in liposomes showed a synergistic effect against P. aeruginosa, by enhancing its penetration into sputum and inhibition bacterial population into biofilms structure. Furthermore, the formulation reduced toxic side effects of BiEDT on lung epithelial cells as indicated by (3-(4,5-dimethylthiazol-2-Yl)-2,5- diphenyltetrazolium bromide (MTT) and lactate dehydrogenase (LDH) assays [27,32]. The authors reported that liposomal BiEDT-encapsulated tobramy- cin reduces P. aeruginosa quorum sensing signaling molecules and production of lipase, chitinase and protease in vitro via fusion mechanism. The efficacy of liposomal formulations of different surface charged encapsulated clarithromycin were investigated against P. aeruginosa clinical isolates from CF patients. Liposomal formulations improved the MIC and MBC against clinical isolates compared with free formulation. Although neutral liposomes was more effective than free formulation, positively and negatively charged liposomes eliminated the bacterial population within the biofilm and were more effective in reducing virulence factors and bacterial motility. Liposomal meropenem was also tested against

IJARSCT
ISSN (Online) 2581-9429
International Journal of Advanced Research in Science, Communication and Technology (IJARSCT)
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Impact Factor: 7.301

sensitive and resistant strains of P. aeruginosa in vitro and showed an improvement in bactericidal activity of the encapsulated drug as the MIC results were two- to four-times lower than the MICs of free meropenem for sensitive strains. Benzyl penicillin-loaded liposomes inhibited the growth of a penicillin-sensitive strain of S. aureus at lower concentration and shorter exposure time than the free drug.

Application of liposomes is an effective therapeutic delivery system in fungal infections. Polyene antibiotic such as amphotericin B are utilized in treatment of candidosis and aspergillosis systemic infections. The mechanism of action of amphotericin B involves binding to ergosterol, a major sterol molecule in fungal membranes, resulting in changes to mem- brane permeability that leads to metabolic disruption, osmotic imbalance, and as a consequence, cell death. The conven- tional amphotericin B with deoxycholate as a surfactant is asso- ciated with significant toxicities including infusion-related reactions, nephrotoxicity and hypokalemia. However, liposome-loaded amphotericin B appears to have less nephro- toxicity than the conventional formulation and amphotericin B lipid complex

IX. CONCLUSION

Wealth of data on the use of liposomes as an effective drug Delivery system in medicine industry has appeared in recent Literature. Liposomes have also drawn great interest from Research scientist as a suitable model for investigation involv- Ing biological membrane structure and function. Several of The liposomes biological and physicochemical properties Including biocompatibility and biodegradability contribute To their success in the pharmaceutical industry. Furthermore, Encapsulated agents in liposomes can be protected from the Host metabolic enzymes and other internal environmental ele- Ments. Liposomes can also prolong the drug effect by provid- Ing a sustained release of the bioactive compound in the body. Most importantly, they can carry any compound regardless of Their chemical affinity as hydrophilic drugs can be encapsu- Lated in the aqueous core whereas lipophilic agents are carried Within the lipid bilayers. Several methods have been developed to prepare ideal lipo- Somes for different anatomic sites and administration routes. Investigating liposomal size, lamellarity, zeta potential and EE have been the areas of concern to improve the shelf life And stability of liposomal formulations. Liposomes can be Administered through different routes depending on the Affected body system. Coupling the liposomes with specific Binding partners and markers leads to enhanced accumulation Of encapsulated agents at the site of interest. In vitro and In vivo studies with such compounds indicate improved Drug pharmacokinetics, pharmacodynamics and efficacy as Well as a reduction in unwanted drugs side effects.

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Volume 3, Issue 2, March 2023
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