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Review Article

Liposomes, Protein and Peptide Drug Delivery Systems

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ABSTRACT

Liposomes play a pivotal role in drug delivery, particularly in the context of proteins and peptides. This abstract explores their application as carriers for these bioactive compounds, highlighting the challenges and advancements in the field. The encapsulation of proteins and peptides within liposomal structures enhances their stability, prolongs circulation time, and facilitates targeted delivery. Various methods of liposome preparation and surface modifications are discussed, addressing issues like immunogenicity and release kinetics. The integration of nanotechnology with protein and peptide drug delivery holds promising prospects for improving therapeutic outcomes and reducing side effects. This abstract provides a concise overview of the current state and future directions in this dynamic and evolving field.

INTRODUCTION

Phospholipids spontaneously form a closed structure with an interior aqueous environment surrounded by phospholipid bilayer membranes when they are dispersed in water. This vesicular system is known as a liposome[1]. Liposomes are a type of small, spherical vesicles that can be made from membrane proteins, sphingolipids, glycolipids, cholesterol, and non-toxic surfactants. Liposomes are a type of drug carrier that may hold a wide range of molecules, including plasmids, proteins, nucleotides, and tiny drug molecules. About 40 years ago, A.D. Bangham made the discovery of liposomes, which are now a useful tool in biology, biochemistry, and medicine[2]. The aqueous compartment of liposomes has been employed as a carrier to transport a wide range of chemicals since the 1960s. Different liposome compositions, sizes, charges, and lamellarities can be achieved through formulation and processing. Liposomal versions of antifungal and antitumor medications have been sold to consumers thus far[3]. In the 1970s, liposomes were shown to have clinical potential as a medium for replacement

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therapy in cases of genetic lysosomal enzyme deficits. Significant advancements in the field of liposome stability during the 1970s and 1980s allowed for prolonged liposome circulation periods following intravenous administration, which improved liposome biodistribution[4]. Liposomes are spherical vesicles with an aqueous phase within that are made of phospholipid bilayers. These amphiphilic self-assembled structures have been used as a model for real cell membranes because they mimic the lipid membranes seen in the cellular morphology of many living species[5]. Liposomes can be categorized into three groups based on their size and lamellarity: (i) unilamellar vesicles (ULVs), (ii) multilamellar vesicles (MLVs), and (MVVs) multivesicular vesicles. Depending on their size, ULVs are further separated into three categories: giant unilamellar vesicles (GUVs), large unilamellar vesicles (LUVs), and tiny unilamellar vesicles (SUVs), with sizes ranging from >1 µm to <100 nm. According to reports, the phospholipid bilayer's thickness is approximately 4 nm, and it is influenced by the type of phospholipid, temperature, and cholesterol concentration[6]. Because of their size and capacity to simultaneously encapsulate hydrophilic and hydrophobic bioactive compounds, liposomes have drawn increased attention in recent years[7]. Liposomes have been used in the food, pharmaceutical, and cosmetic industries to provide targeted delivery and controlled release, as well as to increase the stability, solubility, bioaccessibility, and/or bioavailability of bioactive compounds. For the oral delivery of bioactive substances like asenapine maleate (an antipsychotic medication), exemestane (an anticancer hormone therapy), icariin, antidiabetic peptides, and curcumin, several studies have suggested liposomal formulations[8].

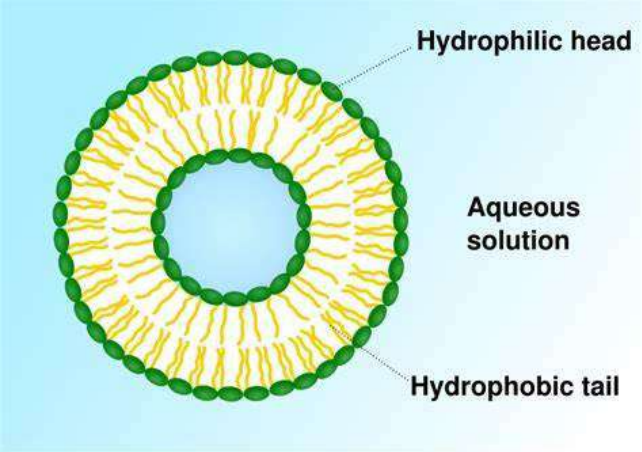

Fig no.1. Liposome

Basic properties of Liposome

Liposomal particles, also known as lipid vesicles, are primarily made up of (phospho)lipid molecules, which are the building blocks of enclosed lipid bilayers or lipid-drug sheet-disk complexes. Many formulations use synthetic versions of natural phospholipid, primarily phosphatidylcholine, despite the fact that the lipid constituent may vary. As a primary membrane building component, phosphatidylcholine (neutral charge) with fatty acyl chains of various lengths and saturation levels is present in the majority of liposome formulations approved for use in humans. In order to control stiffness and lessen serum-induced instability—which is brought on by serum protein binding to the liposome membrane—a portion of cholesterol (30 mol%) is frequently added to the lipid formulation. The differences in liposome size, charge, surface hydration, membrane fluidity, and clearance of lipid-associated drugs are explained by cellular and physiological mechanisms.

Surface charge

Liposomes can have a positive, neutral, or negative charge on their surface depending on the lipid and phospholipid head group composition. Target cell interaction and liposome uptake are influenced by the type and density of charge on the liposome surface, as well as the stability, kinetics, and extent of biodistribution[9].

Surface hydration

Hydrophilic polymers can be used to alter the liposome membrane's surface in order to decrease aggregation and prevent recognition by RES. This tactic is also known as steric modification or surface hydration. Gangliosides, like GM1, or lipids chemically conjugated to hygroscopic or hydrophilic polymers, typically poly(ethyleneglycol) (PEG), are frequently used to modify surfaces. PEGylation of proteins is comparable to this technology. Rather than reducing immune recognition and speedy clearance by conjugating PEG to therapeutic proteins like adenosine deaminase (Alderase, for treatment of severe combined immunodeficiency syndrome) to decrease immune recognition & fast clearance[10]. PEG is coupled to phosphatidylethanolamine's terminal amine. An additional layer of surface hydration is provided by the hydrophilic polymers that are present on the liposome membrane surface[11].

Fluidity of lipid membrane

Below the lipid phase transition temperature (Tc), lipid bilayers and liposome membranes display a well-ordered or gel phase, and above the Tc, they display a disordered or fluid phase. The temperature at which equal amounts of the two phases coexist is known as the lipid phase transition, or Tc. Liposome leakiness reaches a maximum at a temperature that equals Tc[12]. The permeability, aggregation, protein binding, and, to a lesser extent, liposome fusion are all governed by the phase behavior of a liposome membrane. The length and type (saturated or unsaturated) of the fatty acid chains determine the Tc, which means that lipid combinations and selection can affect the fluidity of bilayers. For example, adding cholesterol to the bilayer at low concentration increases transmembrane permeability, while adding more cholesterol (> 30 mol%) can prevent phase transition and reduce membrane permeability at temperatures higher than Tc[13].

Application of Liposome

Over the past 30 years, there has been a significant shift in the field of liposome research. These days, a vast array of varied sizes, phospholipid and cholesterol compositions, and surface morphologies that are appropriate for a wide range of applications can be engineered. Different liposome-cell interactions result in the association of liposomal components with the target cell. Tomography can be used to target the liver and spleen with the liposome carrier and distinguish between tumorous and normal tissue. Liposomes are very useful in transdermal drug delivery systems. When a liposomal drug delivery system is used to target a tumor cell, the drug's toxicity is reduced and its effectiveness is increased. The attachment of an amino acid fragment, such as an antibody, protein, or appropriate fragment that targets a particular receptor cell, allows the liposome to be directed to the site of action. Delivery vector for liposomal DNA and advancement enhancement Some of the safest and potentially most effective transfer vectors currently in use are LPDI-I and LPD-II. The use of liposomes in gene therapy has increased efficacy, as has DNA vaccination. The liposomal drug delivery system has been designed to work with a variety of drug delivery applications.

- Boosting the solubility of medications (doxorubicin, minoxidil, paclitaxel, cyclosporins, and amphotericin B)
- Preventing sensitive drug molecules, such as ribozymes, DNA, RNA, arabinosa, cytosine, and antisense oligo nucleotides
- Stimulate the absorption of antimicrobial, antiviral, and anticancer medications within cells
- Altered pharmacokinetic and biodistribution (drug released over an extended period of time but with a brief half-life in the circulation).

Examples of recent developments in liposomal drug delivery systems:

1. Liposome for respiratory drug delivery system

Liposomes are frequently used to treat various respiratory conditions. Compared to regular aerosol, liposomal aerosol has several advantages. enhanced stability in the large aqueous core, decreased toxicity, avoided local irritation, and sustained release. There are currently several injectable liposome-based products available on the market, such as Myocet, Fungisome, and Ambisome. Liposomes can be inhaled in either a liquid or dry form, with the drug being released during nebulization. Drug powder liposomes can be created by spray drying or milling[14,15].

2. Liposomes in eye disorder

The majority of anterior and posterior segment disorders have been treated with liposomes. Dry eyes, keratitis, endophthalmitis, uveitis, corneal transplant rejection, and proliferative vitro retinopathy are among the eye diseases. In developed nations, retinal diseases are the main cause of blindness. Liposomes are employed as vehicles for monoclonal antibodies and genetic transfection. Retinal and cloroidal blood vessel stasis, angiography, and selective tumor and neo-vescular vessel blockage are among the conditions treated with the most recent therapeutic techniques, which include applying a focal laser to heat and causing the release of liposomal drugs and dyes. Up until now, two patent drugs have had their liposomal drug formulations approved; additional products are undergoing clinical trials[16].

3. Liposomes for brain targeting

Recent studies have examined liposomes as a possible drug delivery system for the brain due to their biocompatible and biodegradable properties. Both broad and narrow-diameter liposomes (diameters of 100 nm) freely diffuse through the blood-brain barrier (BBB). However, it's possible that receptor-mediated or absorptive-mediated transcytosis will transfer a small unilamellar vesicles (SUVS) couple to brain drug transport vectors across the blood-brain barrier. The recently developed cationic liposome demonstrates how this structure undergoes absorptive mediated endocytosis within cells[17,18].

PROTEIN AND PEPTIDE DRUG DELIVERY SYSTEMS

INTRODUCTION

A novel drug delivery system and novel approach to drug delivery is the protein and peptide. The most prevalent materials in biological cells and living systems are proteins and peptides. Immunoglobulins, enzymes, structural elements, and hormones all play a part in it. Participating in multiple metabolic processes, immunogenic defense, and various biological activities are also crucial. One of the most prevalent organic molecules in the biological system is a protein; the word "protein" was initially used by Berzelius. The Greek word proteios, which means "holding the first place," is where the word "protein" originates. Peptide bonds hold together the high molecular weight mixed polymer of alpha amino acids that make up proteins[19,20]. Proteins are primarily made up of carbon, nitrogen, oxygen, and sulfur molecules. Peptide bonds, which hold together molecules with linear chains of amino acids, are what are known as protein bonds. The condensation product of alpha amino acids is known as a peptide. The condensed alpha carboxyl group of one amino acid molecule is the alpha amino group of another amino acid molecule. All living cells contain protein, which serves as a nutritional component and aids in body building. It is a crucial molecule for the cells of plants and animals[21]. Proteins primarily contain enzymes that catalyze biological reactions. These enzymes are useful for the transportation of genes and metabolites. It can be used to give tissues and cells a specific shape and strength. Controlling the temperature, PH, osmotic pressure, and metabolic

pathways is one of its most significant applications. Blood sugar is regulated by the protein insulin.It is crucial for the development of muscles and for mechanical tasks. Two amino acids are condensed to form dipeptides in the case of peptides, three to form tripeptides, four to form tetrapeptides, and peptides containing two to twenty amino acids are polypeptides. Proteins are polymers made up of 100 or more amino acids[22,23]. Proteins are divided into two categories: those based on their solubility and those based on the complexity of their structures. In the first instance, they are divided into two kinds according to their solubility. Proteins that are soluble in water or common salts are referred to as globular proteins, whereas proteins that are soluble in water or common solvents are referred to as fibrous proteins[24]. In the second instance, based on complexity There are three different kinds of proteins. First, there are simple proteins, which only contain one amino acid; second, there are conjugated proteins, which can contain both amino acids and non-protein components; and third, there are derived proteins, which are products of hydrolysis created when physiological agents, such as heat, chemicals, and enzymes, act on protein molecules[25].

Needs:

1. Peptides and proteins play a crucial role in biological cells and organic molecules[26].
2. Diabetes mellitus is one of the diseases caused by the absence of proteins and peptides (A result of insufficient levels of the protein Insulin)[27].
3. These days, protein- and peptide-based medicines also use hybridoma and R-DNA technology[28].

Advantages:

1. RBC synthesis is the primary use of erythropoietin[29].
2. Heart attacks and strokes are treated with the protein tissue plasminogen activator.
3. Labor pain is treated with oxytocin.
4. Bradykinin stimulates peripheral blood flow.
5. Somatostatin reduces stomach ulcer bleeding.
6. Ovulation is induced by gonadotropin.
7. Insulin keeps blood sugar levels stable[30].

Functions:

1. The movement and preservation of biological and small molecules.
2. Coordinated movement through contraction of muscles.
3. The fibrous protein's mechanical support.
4. Nerve impulse production and transmission.
5. The catalysis of biochemical reactions by enzymes.
6. The defense of the immune system by antibodies.
7. Hormone regulation of growth and differentiation[31].

Properties of Proteins & Peptide

The most prevalent biological and organic molecule is a protein; it can form a colloidal solution with water and is soluble in it. The systems that are both metabolically and physicochemically stable are proteins and peptides. When using an oral protein and peptide drug delivery system, The rate at which proteins and peptides are absorbed in an oral drug delivery system can be influenced by a number of properties, including Properties of Absorption, Regarding Absorption Properties Particle size and molecular weight, conformational research, stereo specification of three-dimensional arrangements in space, and immunogenicity of medicinal compounds. are impacted by the rate at which peptides and proteins are absorbed in oral drug delivery systems. Another is the drug's physicochemical properties, which include things like its lipophilicity and solubility, which are important factors in drug absorption, as well as its aggregations and hydrogen bonding when taken orally. The primary criterion for drug absorption in oral drug delivery systems is its physicochemical

properties. Metabolic degradation of different forms of protein and peptides through interaction with different proteolytic enzymes and its lower ability to penetrate membranes are the two main problems associated with drug absorption in oral drug delivery systems. All of the criteria related to the properties of the protein and peptide drug delivery system are applicable for determining a variety of issues pertaining to the oral drug delivery system, and it's critical to provide guidance based on these properties in order to avoid issues with drug administration in oral protein and peptide drug delivery systems[32,33].

Pharmaceutical Approaches of Protein & Peptide

It having Four Approaches in following;

1. Chemical Modification
2. Enzyme Inhibitors
3. Penetration Enhancers
4. Formulation Vehicle
5. Mucoadhesive Polymeric System

1. Chemical Modification:

It's critical to chemically modify proteins and peptides in drug delivery systems to enhance membrane permeability and enzymatic stability. It can be utilized to lessen immunogenicity.

It includes two types;

a. Amino acid modifications
b. Hydrophilization

a. Amino acid modifications:

One of the key methods for changing the physiological characteristics of protein and peptide drug delivery systems is amino acid modification, wherein the substitution of D- and L-amino acids is crucial.

Example:

Desmopressin & Deaminovasopressin are important analogs of Vasopressin.

Application:

To improve membrane permeability and preserve enzymatic stability, amino acid modification is crucial.

b. Hydrophilization:

Its approach to the Lipophilic Moieties is significant[34].

Example:

The Palmitoylatios NOBEX INSULIN.

2. Enzyme Inhibitors

The enzymatic approach of the protein and peptide drug delivery systems is represented by the enzyme (protease) inhibitors. With the aid of a range of nutrients, the GIT and liver are crucial in the metabolism of proteins and peptides into smaller fragments of two to ten amino acids. Enzymatic proteolysis. Protease inhibitors are CO-administered in conjunction with peptides and proteins. To modify the environment in order to suppress proteolytic activity and maintain enzyme stability. The There are four categories of enzyme proteases inhibitors: Aspartic Proteases (Pepsin, Rennin, Serinyl Proteases (Thrombin, Trypsin), Cystinyl Proteases (Papain, Endopeptidase), and carboxypeptidase-containing metallo proteases[35].

3. Penetration Enhancers

One of the most crucial ingredients in the formulation of proteins and peptides is a penetration enhancer, which breaks down mucosal barriers and improves the membrane penetration of large macromolecules like proteins and peptides. A variety of chemical classes, including surfactants (Polysorbate, SLS, Pluronic F-68), chelating agents (EDTA), fatty acids (Sodium Carprate), mucoadhesive polymeric systems (Thiomers, Cellulose Derivatives), and phospholipids (PC), are primarily employed as permeation enhancers. The fundamental working principle of penetration enhancers is that the molecules of detergent and surfactant increase the transcellular transport of the drug material, which in turn causes the lipid bilayer of the lipid membrane to break down and become more permeable[36].

4. Formulation Vehicles

Oral delivery of protein and peptides can be accomplished through the use of a variety of carrier systems, such as the Protein and Peptide Drug Delivery System;

i. Dry Emulsion
ii. Microspheres
iii. Liposomes
iv. Nanoparticles

I. Dry Emulsion:

It is a crucial application in drug delivery systems to stop multiple emulsions from becoming unstable during long-term storage. the innovative method where dry emulsions take the place of multiple emulsions. The techniques of spray drying, lyophillization, and evaporation are used to prepare dry emulsion. It is crucial to apply PH-responsive polymers, such as HPMCP, during the dry emulsion preparation process to ensure that the emulsions are enteric coated and site-specific.

II. Microspheres:

Microspheres are the uniform drug distribution used in protein peptide oral drug delivery. The PH-responsive microspheres are primarily employed in oral administration to guard against proteolytic degradations in the stomach and upper section of the small intestine.

III. Liposomes:

Liposomes are tiny, microscopic vesicles with an entirely lipid-based membrane enclosing an aqueous volume. Insulin degradation in intestinal fluid was totally inhibited by using PEG and the sugar chain portion of mucin to encapsulate the insulin in liposomes, a drug delivery system. When liposome molecules are partially coated with PEG or mucin, the uncoated form of the liposomes is suppressed, increasing the stability of the gastrointestinal tract and providing resistance against salt digestion.

IV. Nanoparticles:

The particles known as nanoparticles are 10-1000 nm-sized colloidal structure at the nanoscale. The intestinal epithelium absorbs particles in the nanometric size range unaltered, making them less vulnerable to enzymatic degradation. The GI tract's absorption of the nanoparticle system is influenced by the surface charges and particle size[37].

5. Mucoadhesive Polymeric Systems

In order to preserve the therapeutic efficacy of the mucoadhesive polymeric system and avoid the issues related to presystemic metabolism, or first pass metabolism, it is essential. The duration of the drug delivery system's stay at the site of action and the rate at which the drug clears[38].

Example:

Thiomers, derivatives of polyacrylic acid, and derivatives of cellulose are a few examples.

Stability Aspects

The protein degradation pathways in this drug delivery system underpin two pathways of protein and peptide molecule degradation, which they have specified as follows:

1. Physical Degradation Pathways
2. Chemical Degradation Pathways

1. Physical degradation pathways

The main indicator of the protein molecules' physical instability in the event of physical degradation. When it comes to globular proteins, the hydrophilic and hydrophobic residues are buried inside. It's interacting with the aqueous solvents. The term "denaturation of Protein Molecule" describes how a protein molecule loses or damages its globular structure, which causes the protein to unfold. The environment in which protein molecules are found, such as temperature, pH, the presence of hydrophobic surfaces, or the introduction of interfaces through the addition of organic solvents, can all contribute to physical denaturation.

2. Chemical Degradation Pathways

The protein and peptide's chemical instability can result in the four types of reactions listed below;

a. Oxidation
b. Deamination

c. Peptide bond hydrolysis
d. Disulfide exchange

a. Oxidation

One of the most significant chemical instabilities of peptide and protein molecules is oxidation. The side chains of proteins and peptides that contain amino acids are prone to oxidation. This oxidation is caused by oxygen molecules in the atmosphere, different kinds of metal ions like iron or copper, and a number of reagents like hydrogen peroxides.

b. Deamination

This particular form of instability is caused by the hydrolysis of the amide side chain of specific amino acid residues, primarily glutamine and asparagine, which is referred to as deamination. It has been primarily demonstrated that certain conditions, such as variations in pH and temperature, facilitate the deamination process of biological therapeutic proteins and peptides.

c. Peptide bond hydrolysis

Aspartic acid residues are heated to 90–1000 C in PH 4 (acetate) during this peptide bond hydrolysis process, which results in the hydrolysis of Asp–X bonds and the loss of biological activity.

d. Disulfide Exchange

There are cystein residues from disulfide bonds in the therapeutic protein. Important elements of the proteins' structural integrity are these newly formed bonds. Protein molecules' three-dimensional structure and biological activity are altered when peptide bonds are linked incorrectly[39].

Application:

1. CVS acting drugs Protein & Peptide: Bradykinin, captopril, and angiotensin 2 antagonists are essential for lowering blood pressure and enhancing peripheral circulation in the treatment of heart failure[40].
2. CNS active Protein & Peptide: (B-endorphin, cholecystokinin) is essential for reducing hunger and alleviating pain[41].
3. GI-active Protein & Peptide: (Pancreatic enzymes, gastrin antagonist) is crucial for lowering gastric acid secretion and for digestive supplements[42].
4. Immunomodulation of the Protein & Peptide: (Bursin, Cyclosporin, and Interferon) is critical for the specific differentiation of B cells. inhibits T-lymphocyte functions that enhance killer cell activity[43].
5. Metabolism Modulating Protein & Peptide: It's crucial to treat diabetes mellitus and diabetes insipidus with insulin and vasopressin[44].

CONCLUSION:

The comprehensive review highlights the pivotal role of liposomes in drug delivery, particularly for proteins and peptides. It explores various aspects, including liposome types, surface modifications, and their application in different drug delivery systems. The integration of nanotechnology with protein and peptide delivery holds promise for therapeutic advancements and reduced side effects. The section on protein and peptide drug delivery provides an in-depth understanding of their importance in biological systems. The review covers their functions, needs, advantages, and properties. Different pharmaceutical approaches, such as chemical modification, enzyme inhibitors, penetration enhancers, and formulation vehicles, are discussed in detail. The stability aspects, including physical and chemical degradation pathways, provide valuable insights into maintaining the efficacy of protein and peptide drug delivery systems. Overall, the abstract and subsequent sections offer a concise overview of the current state and future directions in liposomal drug delivery and protein/peptide drug delivery systems, contributing to the dynamic and evolving field of pharmaceutical research.

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