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A COMPREHENSIVE REVIEW: MUCOADESIVE LIPOSOMAL DRUG DELIVERY SYSTEM

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ABSTRACT

Mucoadhesion is the term used to describe the adhesion between two materials, at least one of which is a mucosal surface. In the past few decades, mucosal drug delivery has been receiving a lot of attention. Mucoadhesive dosage forms allow for extended retention at the site of application as well as a controlled rate of drug release to achieve better therapeutic outcomes. Liposomes have been considered promising and versatile drug vesicles. Now a days, the preparation of mucoadhesive liposomal drug delivery system, it is able to improve the bioavailability of poorly absorbed oral drugs by prolonging their gastric and intestinal residence time, through facilitating the intimate contact of the delivery system with the absorption membrane. Liposomes are simple microscopic vesicles in which an aqueous volume is entirely enclosed by a membrane compose of a lipid moiety and are well known to alter the bio-distribution of entrapped substances by protecting the enclosed materials. Therefore, the preparation of mucoadhesion has attracted a great ideal of attention in the many pharmaceutics sectors. The mucoadhesive drug delivery system has many benefits that make it an innovative method for the local and systemic administration of various medications.

KEYWORDS: Mucoadhesion, Liposomes, Membrane, Drug Delivery.

INTRODUCTION

MUCOADHESIVE DRUG DELIVERY SYSTEM

Any link that forms between two biological surfaces or between a biological surface and a synthetic surface is referred to as bio adhesion. The term "bio adhesion" in the context of bio adhesive drug delivery refers to the adhesion between synthetic or natural polymers and soft tissues, such as the mucosa of the gastrointestinal tract. When a link is established with mucus, bio adhesion and mucoadhesion can be used interchangeably. A state known as mucoadhesion occurs when two components, one of which is biological in origin, are kept together over an extended length of time by interfacial forces. Mucoadhesion is the word used when a bond is formed with a mucosal surface, while bio adhesion, in general, and refers to sticky interactions with any biological or biologically generated substance.[1]

MECHANISM OF MUCOADHESION

To induce a close contact and increase the surface contact, the mucoadhesive dosage form has to spread over the substrate and aid in the diffusion of mucus chains.[2] And repulsion forces appear; hence, for a mucoadhesion to be successful, the attraction forces need to be stronger.[3] The first two steps i.e. contact stage and consolidation stages are shown in Fig.[4]

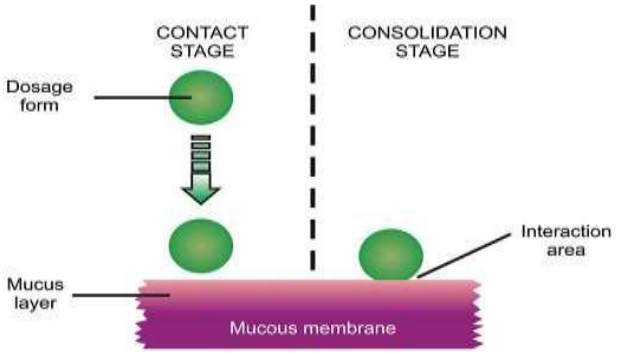

Fig. No. 01: Mechanism of mucoadhesion.

THE FOLLOWING STAGES OF THE MUCOADHESION PROCESS

Step 1: Contact Stage

When the polymer travels beyond the mucosal membrane to make intimate contact with the substrate, the wetting and swelling stage follow.[4] Because the constituents of polymer have a preference for water, polymer swells.[5] The distribution method in vaginal, buccal, or ocular formulations is mechanically bonded to the membrane.[6] In other situations, such as when the formulation is supplied via the nasal route, the deposition is caused by the aerodynamics of the organ. Peristaltic movements within the gastrointestinal system may facilitate this interaction.[7] The particle encounters both repulsive and attractive forces if it moves toward the mucosal surface. In order for contact to occur, the particles must overcome the repulsive barrier.[8]

Step 2: Interpenetration Stage

Glycoproteins are large molecular weight polymers that are present on the surface of mucous membranes.[8] The mucosal and bioadhesive polymer chains intertwine and create adhesive bonds in the second step of the bioadhesive bond formation process.[9] The degree of interpenetration between the two polymer groups determines the bond strength. A strong chemical connection forms if the two polymers have similar chemical structures, that is, if they are both hydrophilic.[10]

Step 3: Consolidation Stage

During the consolidation process, mucoadhesive materials are activated in the presence of moisture. This causes the mucoadhesive molecules to break loose and re-bond via weak hydrogen and Van der Waals bonds. The consolidation stage is essentially explained by the ideas of diffusion and dehydration. The mucoadhesive molecules and the mucus's glycoproteins interact with one another through chain entanglement and the formation of secondary bonds, according to the theory of diffusion.[11] The idea of dehydration states that materials that readily gelify in an aqueous environment can dehydrate mucus by creating an osmotic pressure difference when they come into contact with it, as illustrated in Fig. below. The concentration gradient causes water to be pulled into the formulation until the osmotic equilibrium is reached, which increases the contact time.[12]

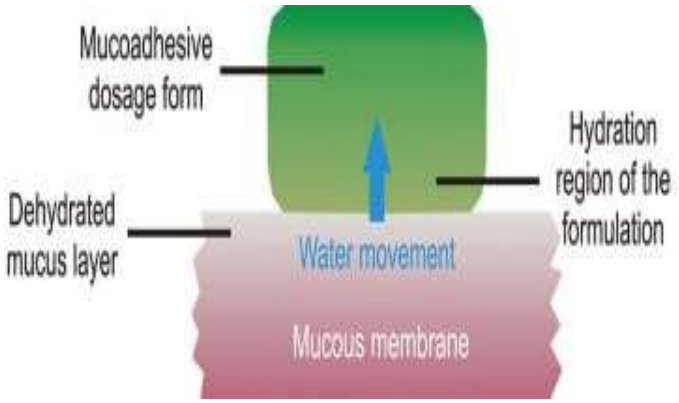

Fig. No. 02: Dehydration theory of mucoadhesion.

Advantages of mucoadhesive drug delivery

- The buccal drug delivery has a high level of patient acceptability since, in comparison to other non-oral routes; it offers a relatively quick onset of action.
- Better patient compliance as a result of dosage forms' ease of use compared to injections and lack of unpleasant side effects Because of the mucosal membranes' high vascularization, administering and removing dosage forms is simple.
- The use of mucoadhesive polymers of "SR" grades can result in sustained medication delivery.
- The rate of drug absorption is quicker due to the great amount of perfusion.
- The potential negative effects of oral delivery, such as nausea and vomiting, can be fully avoided
- Drugs with low oral bioavailability can have their bioavailability increased by designing their mucoadhesive delivery methods, making them easier to administer to unconscious and uncooperative patients.[13,14,15]

Disadvantages of mucoadhesive drug delivery

- The rate of drug absorption is quicker due to the great amount of perfusion.
- The potential negative effects of oral delivery, such as nausea and vomiting, can be fully avoided.
- Drugs with low oral bioavailability can have their bioavailability increased by designing their mucoadhesive delivery methods
- Making them easier to administer to unconscious and uncooperative patients.[13,14,15]

LIPOSOMAL DRUG DELIVERY

Alec D. Bangham created liposomes synthetically for the first time in England in 1961. He discovered that phospholipids and water mix to form a sphere because one end of each molecule is soluble in water while the other is not.[16] Liposomes are closed, spherical entities made of lipid bilayers that curve and partially encapsulate the surrounding fluid inside. Liposomes can be as small as 20 nm or as large as several micrometres.

They are made up of one or more membranes, either nonconcentric or concentric, with a thickness of roughly 4 nm.[17] The innovative medicine delivery technology known as liposomes seeks to deliver the medication right to the site of action. Both hydrophilic and lipophilic molecules may be accommodated by them in order to prevent medication degradation and release the active components in a regulated way.[18]

Phospholipids, amphiphilic molecules with a lipid-soluble, hydrophobic tail section and a water-soluble, hydrophilic head region, are the primary components of liposomes. Because of this phospholipid feature, liposomes have special qualities including self-sealing in aqueous environments, which makes them an excellent carrier system with uses in pharmaceutics, food, cosmetics, and agriculture.[16]

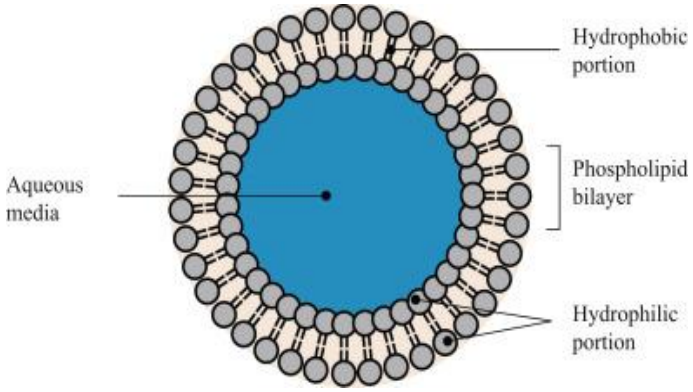

Fig. No. 03: Structure of liposomes.

ADVANTAGES OF LIPOSOMES

- Offers liposomal doxorubicin, a specific passive target for tumour tissues.
- Enhanced effectiveness and therapeutic index.
- Enhanced stability through encapsulation.
- A decrease in the agents' toxicity that are encapsulated.
- The effect of site avoidance.
- Better impacts on pharmacokinetics.
- Adaptability to combine with ligands unique to certain sites to accomplish active targeting.

DISADVANTAGE OF LIPOSOME

- The expense of production is substantial.
- Seepage and amalgamation.
- Drug/molecules enclosed in a capsule.
- Minimal half-life.
- Issue with stability.[19]

MECHANISM OF LIPOSOMES FORMATION

Phospholipids, which are amphiphilic molecules (having a hydrophilic head and a hydrophobic tail), are the most basic or significant components of liposomes. The hydrophobic portion is made up of two fatty acid chains with 0–6 double bonds in each chain and 10–24 carbon atoms.[20] The hydrophilic portion is primarily made up of phosphoric acid coupled to a water-soluble molecule. When these phospholipids are distributed or dispersed in an aqueous medium, they arrange themselves so that the fatty acid groups face one another and the polar head group faces outward toward the aqueous region, resulting in the formation of lamellar sheets and the final spherical or vesicle-like structures known as liposomes. Along with protecting or keeping the non-polar section (which is positioned at an angle to the membrane surface) safe, the polar portion stays in contact or residues in the watery zone. When water is added to phospholipids, additional energy is added through sonication, shaking, heating, homogenization, etc.[21] To attain or reach a thermodynamic equilibrium in the aqueous phase, bilayer vesicles are formed as a result of the hydrophilic/hydrophobic interactions between lipid–lipid and lipid–water molecules.[22]

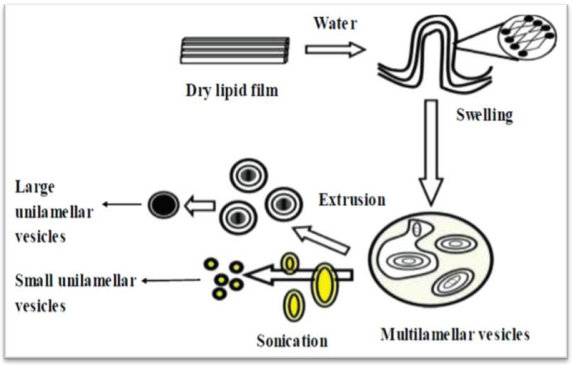

Fig. No. 04: Mechanism of Liposome Formation.

STRUCTURAL COMPONENTS OF LIPOSOMES[23,24,25,26]

The major constituents of liposome include

- Phospholipids
- Cholesterol.

Table No. 01: Constituents of liposome.

PHOSPHOLIPIDS (Example)	CHOLESTEROL (Example)
Phosphatidylcholine	Alkyl fatty acid
Phosphatidylethanolamine	allyl fatty acid
phosphatidylserine	
Dioleoyl phosphatidyl choline	

CLASSIFICATION OF LIPOSOMES

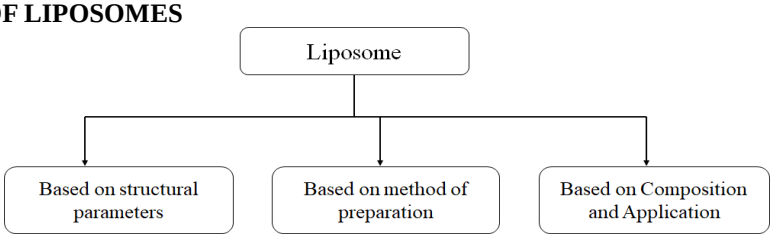

Fig No 05: classification of liposomes.

BASED ON STRUCTURAL PARAMETERS

Vesicular type	Abbreviation	Diameter range	Number of lipid bilayer
Unilamellar vesicle	UV	All size range	1
Small unilamellar vesicle	SUV	20-100nm	1
Medium unilamellar vesicle	MUV	>100µm	1
Large unilamellar vesicle	LUV	>1000µm	1
Giant unilamellar vesicle	GUV	>1µm	1
Oligolamellar vesicle	OLV	>0.1-1µm	5
Multilamellar vesicle	MLV	>0.5µm	5-25
Multivesicular vesicle	MV	>1µm	Multicompartmental structure

Fig. No. 06: Classification of liposomes (Based on structural parameters).

METHODS OF PREPARATION OF LIPOSOMES

- **Passive loading technique:** Involves loading of entrapped agents before or during themanufacturing process.
- **Active loading technique:** Involves loading of certain type of compounds into the liposomes after the formation of intact vesicles.

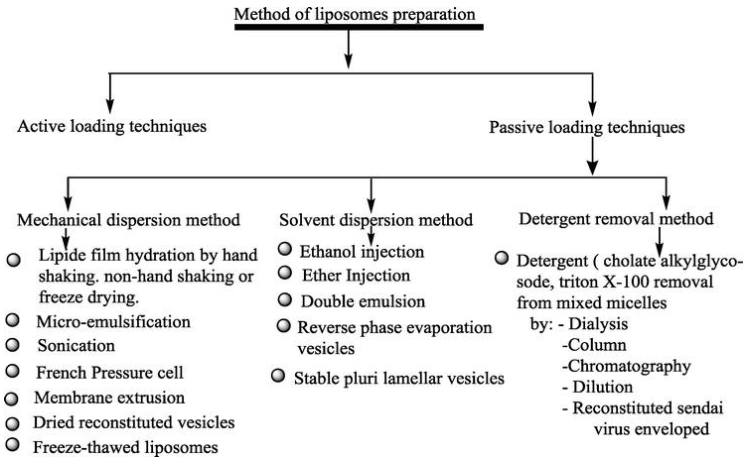

Fig. No. 07: Method of liposome preparation.

MECHANICAL DISPERSION METHODS OF PASSIVE LOADING

a. The method starts with an organic solvent-based lipid solution and culminates in lipid dispersion in water.
b. The lipids are co-dissolved in an organic solvent to blend different components, which is subsequently removed using vacuum-assisted film deposition.
c. Aqueous buffer is used to hydrate the solid lipid mixture following solvent removal.
d. Lipids expand and hydrate on their own to produce liposomes.
e. The post-hydration processes consist of high-pressure extrusion, freeze-thawing, sonication, and vertexing.

Thin film hydration technique/ Hand shaken MLV'S

This process results in MLVs. Using a round-bottomed flask, phospholipids are dissolved in an organic solvent such as chloroform: methanol in a 2:1 v/v ratio. After that, the RBF is fastened to the rotating evaporator and given permission to spin at 60 rpm. Consequently, the organic solvent evaporates. As a result, a thin, uniform lipid coating forms on the RBF's sidewalls. Utilizing nitrogen gas, the leftover solvent is eliminated. Using an aqueous medium, the lipid film that has developed is hydrated. This produces a milky white suspension that is set aside for two hours at room temperature or higher than the lipid transition temperature. Thus, full swelling of the particles takes place, resulting in MLV development.[27,28]

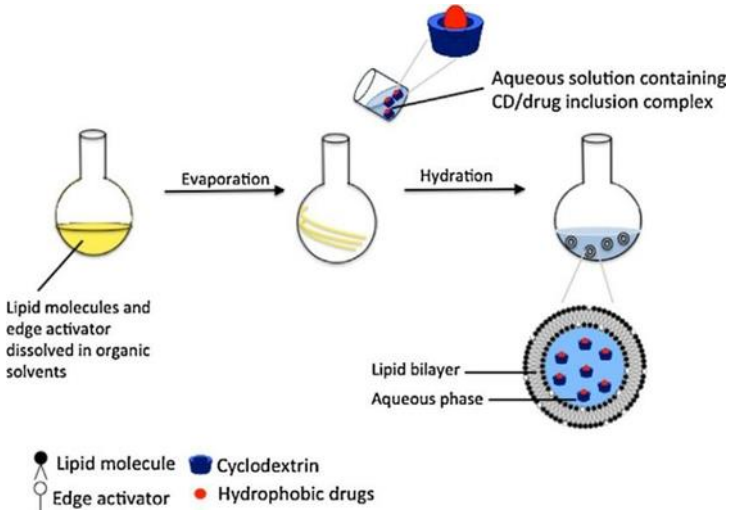

Fig. No. 08: Schematic representation of preparation of liposomes by thin film hydration technique/ Hand shaken MLV'S.

SOLVENT DISPERSION METHOD

1. Ether injection method

Lipids are dissolved using this approach in either ether/methanol or diethyl ether. After that, an aqueous solution containing the substance to be encapsulated is injected with this lipid mixture. This is done at lower pressure or at a temperature between 55 and 65 degrees Celsius. The use of vacuum causes organic solvents to evaporate. At last, liposomes are produced.

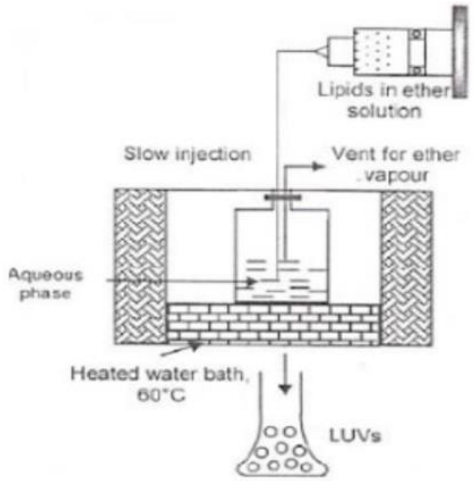

Fig. No. 09: Preparation of liposomes by Ether injection method.

2. Ethanol injection method

Using a fine needle, an excess of saline or aqueous solution is injected with an ethanol solution containing lipids. Subsequently, mixing is done to create SUVs.

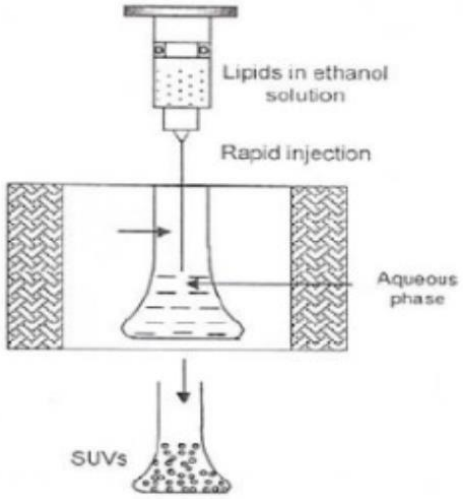

Fig. No. 10: Preparation of liposomes by Ethanol injection method.[29,28]

CHARACTERIZATION/EVALUATION OF LIPOSOMES

The liposomes prepared by various techniques are to be evaluated for their physical, chemical and as well as biological properties.

Table No. 02: Physical characterization.

SL.NO	PARAMETER	METHOD
PHYSICAL CHARACTERIZATION		
1	Entrapment efficiency	Mini column centrifugation, Protamine aggregated method.
2	Vesicle shape & surface morphology	Transmission electron microscopy, freeze fracture electron microscopy.
3	Lamellarity	Small angle X-ray scattering, freeze fracture electron microscopy.
4	Particle size & size distribution	Light microscopy, Transmission electron microscopy, freeze fracture electron microscopy, gel permeation, gel extrusion, zeta sizer.
5	Surface charge	Free flow electrophoresis, zeta potential measurement.
6	Drug release	Diffusion cell, dialysis tube
7	Phase transition behaviour	DSC (differential scanning calorimetry)

Table No. 03: Chemical characterization.

SL.NO	PARAMETER	METHOD
CHEMICAL CHARACTERIZATION		
1	Phospholipid concentration	Bartlet assay, Stewart assay, TLC
2	Cholesterol concentration	Cholesterol oxidase assay, ferric perchlorate method.
3	Lysolectin concentration	Densitometer
4	Phospholipid peroxidation	UV – absorbance, iodometry, GLC
5	Phospholipid HYDROLYSIS and cholesterol auto oxidation	HPLC, TLC
6	PH of liposomal dispersion	pH meter
7	Osmolarity	Osmometer

Table No 04: Biological characterization.

SL.NO	PARAMETER	METHOD
BIOLOGICAL CHARACTERIZATION		
1	Sterility	Aerobic or anaerobic culture
2	Pyrogenisity	LAL test
3	Animal toxicity	Monitoring survival rate, histology and pathology.

STABILITY OF LIPOSOMES

Stability is defined as capacity of particular formulation in a specific container/ closure system to remain with in physical. Chemical, microbiological, therapeutic and toxicological specification.[31]

REVIEW OF LITERATURE

1. **Karn *et al*., (2010),** studied on mucoadhesive liposomal delivery systems and the choice of coating material, which is able to improve the bioavailability of poorly, absorbed oral drugs by prolonging their gastric and intestinal residence time, through facilitating the intimate contact of the delivery system with the absorption membrane. Liposomes loaded with drug atenolol were prepared by the modified ethanol injection method. They concluded the recommend system described in their work for possible oral delivery of peptides and phyto-chemicals.[32]

2. **Khutoryanskiy *et al*., (2018),** reviewed that mucoadhesive drug delivery systemsare desirable as they can increase the residence time of drugs at the site of absorption/action, provide sustained drug release and minimize the degradation of drugs in various body sites. Their study particularly focused on the effect of chemical derivatization on the mucoadhesive properties of chitosan. Additionally, other important properties including water-solubility, stability, controlled release, permeation enhancing effect, and in vivo performance are also described.[33]

3. **Badran *et al*., (2022),** studied on novel Metoprolol-loaded chitosan-coated deformable liposomes in thermo sensitive *in situ* gels for the management of glaucoma. Investigated on integration of chitosan-coated liposomes with thermo sensitive *in situ* gel. Metoprolol is believed to help reduce elevated intraocular pressure. Uncoated and coated liposomes loaded *in situ* gel were prepared and characterized by *in vitro*, *ex vivo*, and *in vivo* studies. Uncoated and coated liposomes loaded *in situ* gel were prepared and characterized by *in vitro*, *ex vivo*, and *in vivo* studies. Uncoated and coated liposomes displayed spherical shapes with nano size range, reasonable entrapment efficiency percentage, and significant bio adhesion. By comparing the chitosan coated and uncoated liposomes, coated liposomes shows a significant mucin mucoadhesion. Among all the gel formulation which shows max of 73.6 ± 4.13% has elevated the intraocular pressure.[34]

4. **Priyanka *et al*., (2019),** investigated on design of mucoadhesive liposomes containing Prednisone. Mucoadhesive liposomes loaded prednisone formulations were prepared by different concentration of lecithin and cholesterol by thin film hydration technique. These formulations were evaluated for entrapment efficiency, particle size, zeta potential, surface morphology and *in vitro* drug release. Highest entrapment efficiency was observed among the formulation was 92% and 94%. The percent drug release from all the formulation was observed as follows F1-88.57%, F2-73.31%, F3-76.29%, F4-90.97%, and F1 coated as a CF1-69.85%.[35]

5. **Parthiban *et al*., (2017),** studied about design a mucoadhesive liposomal system of Repaglinide for the treatment of type - 2 diabetes mellitus. Mucoadhesive liposomal formulations were prepared by using different ratio of lecithin and cholesterol by thin film hydration technique. Particle size and zeta potential of formulation containing soya lecithin and cholesterol ratio 5:2 was found to be 212 nm, -164.9 mV respectively. Coating of liposomes resulted increase in particle size and also increases the zeta potential. Highest entrapment efficiency was observed about 90% and 95%. The percent drug release was observed as follows F1-79.04%, F2- 76.77%, F3- 64.32% and CF1-66.65%, CF2- 62.12%, CF3- 56.54%.[36]

APPLICATION OF LIPOSOMES

1. **Liposomes in pharmaceutical industry:** Amphotericin B and minoxidil are used to treat fungal infections by solubilizing the former. Amphotericin B is used to minimize nephrotoxicity and doxorubicin is used to minimize cardiac toxicity in cancer and fungal infections in order to avoid certain sites. For the long-term effects of hormones, corticosteroids, systemic antineoplastic medications, drug depots in the lungs for cancer, and bio therapeutics.

2. **Liposomes as drug delivery vehicles:** Improved medication solubilization, such as that of minoxidil, cyclosporine, and amphotericin B defence of delicate medication molecules, such as DNA, RNA, and cytosine arabinose increased absorption within cells, for example Antimicrobial, antiviral, and anticancer medications Modified pharmacokinetics and bio distribution, meaning that medications with brief circulatory half-lives can be released gradually or continuously. Elevated therapeutic index, for

example antitumor medications, such as actinomycin D and cytosine arabinoside tri-phosphate (ara-CTP).

3. **Liposomes as a lysosomotropic carrier:** In the treatment of enzyme disorders such as Gaucher's disease (beta glycosidase deficiency) and Pompe's disease (alpha glycosidase deficiency), liposomes have been employed as lysosomotropic carriers. Patients with lysosomal storage diseases can receive a range of lysosomal enzymes encapsulated in liposomes. Liposomes, such as liposomal EDTA, are also used to treat metal toxicity.

4. **Liposomes in anticancer therapy:** DaunoXome®: Advanced Kaposi's sarcoma is treated with daunorubicin-containing DSPC/chol liposomes. Caelyx®/Doxil®: MyocetTM: Doxorubicin containing EPC/chol liposomes is utilized in metastatic breast cancer; doxorubicin with HSPC/chol/PEG-DSPE liposomes is used in advanced Kaposi's sarcoma.

5. **Liposome as anti-infective agents:** Using an Active Targeting Strategy Leishmianiasis is treated with anamycin. Asiaticoside is used to treat leprosy and tuberculosis. Tuberculosis is treated with rifampicin. Method of passive targeting Treatments for meningitis, leishmaniasis, and candidiasis include amphotericin B. Macrophage activation is treated with paziental. Gentamycin is used to treat pneumonias caused by Staphylococci.

6. **Liposome in eye disorders:** Liposomes have been utilized extensively in the treatment of anterior and posterior segment disorders. Dry eyes, corneal inflammation (keratitis), corneal transplant rejection, inflammation of the middle layer of the eye (uveitis), inflammation of the internal coats of the eye (endophthalmitis), and proliferative vitreoretinopathy (PVR), a condition that arises as a consequence of rhegmatogenous retinal detachment (i.e., retinal separation linked to a break, hole, or tear in the sensory retina) are among the eye diseases. "Verteporfin" is one of the liposomal medications that are presently authorized for use in the eyes.

7. **Liposomes as radio diagnostic carriers:** Various imaging methods employ liposomes to precisely detect the locations. Liver and spleen imaging, lymphatic imaging, tumour imaging, blood pool imaging, brain imaging, cardiovascular pathology imaging, visualization of inflammation and infection sites, and bone marrow and ocular vasculature are only a few of their radio diagnostic applications.[37]

CONCLUSION

One of the novel delivery systems is liposomal drug delivery system, which can be used to target and control medication distribution. In recent days, topical liposomal compositions work better and provide safe therapeutic efficacy. This review provides that liposomes are an extremely effective medication delivery mechanism. Both hydrophilic and lipophilic drugs are readily incorporated into the liposomes. Future research on liposome delivery of genes and medications is expected given its promising results. Numerous medications' oral bioavailability is influenced by mucoadhesive drug delivery systems, such as those that extend the drug's residence duration, which boosts absorption. Mucoadhesive dose forms include nasal, vaginal, ocular, and rectal drug delivery systems in addition to the straightforward oral mucosal delivery method.

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