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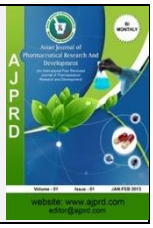

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Review Article

Liposome: A Novel Carrier for Targeting Drug Delivery System

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A B S T R A C T

Targeted drug delivery, sometimes called Smart drug delivery is a method of delivering active molecules to the target site by increasing the concentration of active molecules and produces the desired effects without disturbing the bio-environment. This system is based on a technique that delivers precise amount of an active ingredient for a prolonged period of time to a targeted diseased area inside the body. This helps to maintain the specified plasma and tissue drug levels within the body, thereby preventing any harm to the healthy tissue via the drug. It is advantageous in terms of reduction in the frequency of administration, having a more uniform effect of the drug, reduction of side-effects and reduced fluctuation in circulating drug levels. Among several vesicular drug delivery systems, Liposome have attracted a lot of attention than alternative systems because of several meritable features like excellent chemical and biological stability, good solubilization power, promote intracellular delivery of bio-active molecules, reduce the uptake of macrophages and encapsulate each hydrophilic in addition as lipophilic drug molecules. The focus of this review is to discuss liposome with special emphasis on targeting of drugs.

Key words: Targeted drug delivery system, Encapsulation, Vesicular system, Macrophages

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INTRODUCTION

In traditional drug delivery systems such as oral ingestion or intravascular injection, the medication is distributed throughout the body through the systemic blood circulation. For most therapeutic agents, only a small portion of the medication reaches the organ to be affected, such as in chemotherapy where roughly 99% of the drugs administered do not reach the tumor site. Targeted drug delivery seeks to concentrate the medication in the tissues of interest while reducing the relative concentration of the medication in the remaining tissues. For example, by avoiding the host's defense mechanisms and inhibiting non-specific distribution in the liver and spleen, a system can reach the intended site of action in higher concentrations[1]. Targeted delivery is believed to improve efficacy while reducing side-effects. When implementing a targeted release system, the following design criteria for the system must be taken into account: the drug properties, side-effects of the drugs, the route taken for the delivery of the drug, the targeted site, and the disease[2].

Increasing developments to novel treatments requires a controlled microenvironment that is accomplished only through the implementation of therapeutic agents whose side-effects can be avoided with targeted drug delivery[3].

Among many available targeted drug delivery systems, Liposomes (a class based on phospholipids) have attracted much more attention than other systems due to many meritorious features in delivering the various drugs to the target site[4].Liposomes are self-closed spherical structures, composed of one or several concentric curved lipid bilayer membranes and cholesterol. The word consist of two Greek words 'Lipos' and 'Soma' means fat and body respectively. A liposome is composed constituents that are similar to components of cell membrane. In 1961, liposomes were first discovered in England by Alec D. Bangham, during his study on phospholipids and blood clotting. In his studies, he founded that when phospholipids combined with water, it immediately forms a spherical particle because the one end

of phospholipids molecule is hydrophobic while the opposite end hydrophilic.Due to the amphiphilic character of the lipids, liposome becomes attractive candidates for drug as well as cell delivery.

All Amphiphiles consist of soluble part in non-polar as well as polar solvent.In water solution, the amphiphiles dissolve at first followed by aggregation above certainconcentration by increased entropy of the system[5].The molecular geometry of most lipids can be approximated as cylinders; lipids prefer to self-assemble into bilayer.

According to the solubility of the drug, it may either present in aqueous region orintercession between the bilayers of lipid. Liposomes deliver their content to specific sites by fusing lipid bilayer with cell membrane or other lipoid layer. Liposomes can be categorized as MLV (Multilamellar Vesicles), SUV (Small Unilamellar Vesicles) and LUV (Large Unilamellar Vesicles).

Liposomes can be differentiated from lipid monolayer structure as the one have a clear separation between hydrophilic and hydrophobic compartments. The molecules which are used to form liposomes may be of amphipathic nature. Depending on manufacturing techniques and control of parameters, liposomes may vary in size.

The size range for SUV is 0.02-0.05 µm and for LUV is greater than 0.06 µm and for MLV is 0.1-0.5 µm. nowadays, liposome technology is growing at fastest rate and used in various fields including gene delivery and cosmetics. The ideal characteristics of liposomal formulations include; high drug entrapment efficiency, narrow size distributions, stabilities to a long-term period and be able to provide protection against degradation to the agents that are encapsulated and also shows ideal release. Numerous techniques have been used for preparation of liposomes which may give rise to the different size of vesicles that ranges from 20 nm to several microns (in diameter) and consist of single or more bilayers[6].

Liposomes can entrap chemical agents of different sizes. In choosing the preparation method for liposomes the main focusing point is to select a procedure that yields vesicles of correct size, rigidity and vesicles which show no leakage of entrapped content[7]. In the diseases which affect the phagocyte cells of immune system the liposomal drug delivery systems are very effective because phagocyte cells recognize liposome as foreign invaders then the liposomes are engulfed by the phagocyte cells, accumulate in cells and act on the phospholipid layer and entrapped material are released[8].

Liposomal delivery systems used as a target to the infected tissues and mechanism of action in the human body are in under studies. They have also been used in gene therapy, so as to deliver normal gene as well to replaced one that is responsible for any pathogenesis.

Ideal characteristic of liposomes in drug delivery

Liposome plays a critical role in controlled delivery of drug as well as gene to the target site and the growth of cells within the porous structure or surrounding tissue. The matrix material should be biodegraded at a controllable rate and to provoke a minimal immune and/or inflammatory response in vivo[9]. An ideal drug delivery liposome should fulfill the following requirements:

- Should have acceptable biocompatibility and toxicity profiles.
- Should be free from harmful immune or inflammatory reaction.
- Degradation products should be non-toxic with cell and tissue.
- Should protect the active components from tensile forces.
- Should match with implementation site.
- Stability should retain for longer duration of period.
- Should maintain physical, chemical and biological activity within the body.
- Should be optimum to prevent dose dumping.
- Should have maximum loading capacity.
- Possess relatively easy processability.
- Easy malleability into desired shape.
- Should be capable of producing into a sterile product.
- Should have a reproducible microscopic and macroscopic structure.
- Should be similar to the native extracellular matrix.
- Should have an adequate porosity, pore size distribution and its interconnectivity.
- Should have high degree of porosity for ideal drug release as well as interaction with organs.
- Should be stable at physiological environment.

Structure of liposome

The main part of the liposomes is phospholipids, which are amphiphilic molecules containing water-soluble hydrophilic head section and a lipid-soluble hydrophobic tail. Usually, liposomes are composed of cholesterol and phospholipids.

This special structure of the liposomes creates unique properties in them such as self-sealing in aqueous media and makes them ideal carrier systems with applications in different fields including medicine, immunology, diagnostics, cosmetics, ecology, cleansing, and the food industry[10].

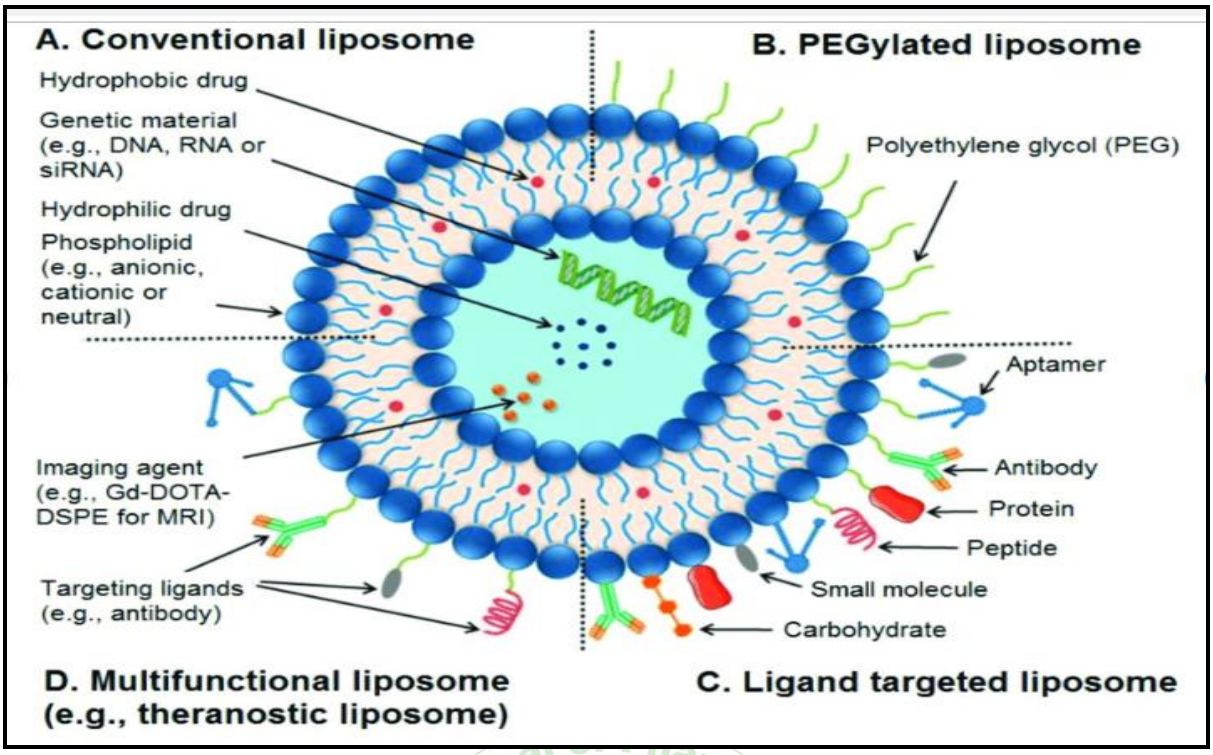

Figure 1: Structure of Liposome

Advantages

- Liposomes are biocompatible, completely biodegradable, non-toxic, flexible, and non-immunogenic for systemic and non-systemic administrations.
- Improved solubility of lipophilic and amphiphilic drugs: The hydrophobic anti-cancer drugs can be incorporated in the lipid membrane of liposome that will increase the solubility of poorly soluble anti-cancer drugs[11].
- Liposome provides selective passive targeting to tumor tissues especially cells of the mononuclear phagocytic system, for example, antimonials, amphotericin B, porphyrins, vaccines, and immunomodulators. Improved solubility of lipophilic and amphiphilic drugs[12].
- Increased potency and efficacy: Nano liposomes can penetrate most of the biological membranes of the body. This results in higher accumulation of drug at the targeted site of action and increases the therapeutic index and efficacy of drug[13,14].
- Flexibility to couple with site-specific ligands to achieve active targeting: Due to adjoint of such site-specific ligands, the drug procreate its effects at the desired site only, and reduces the probabilities of drug-related toxicities[15].
- Higher Stability: Liposome by encapsulating drugs prevents the enzymatic degradation of the drug and causes more drug sustainability in the blood in the circulation[16].
- Decreased toxicity: Liposome by encapsulating drugs reduces the effective dose required for treatment and risk of dose-dependent toxicity; therefore, this improvestreatment safety and efficacy and decreases side effects and adverse events occurring due to high dosage[17].
- Site avoidance effect: Liposome gets poorly accumulated in soft tissues such as kidney and heart; therefore, entrapped drugs in liposome (such as anti-inflammatory drugs, anti-cancer, and anti-infection) can have less destructive effects on the tissues. These result in a site avoidance effect of the drugs[18].
- Improved pharmacokinetic effects: Liposomes can reduce elimination of half-lives. PEG-coated liposome has longer circulation time in systemic circulation and causes slow release of drugs and reduces drug administration and increases the therapeutic index of the drug[19].

Disadvantages

- Their production cost is very high.
- There may be chances of leakage of encapsulated drug or molecules.
- Sometimes there may be chances that phospholipids undergo oxidation and hydrolysis like reaction[20].
- They may have low solubility in aqueous medium.
- They may have stability problem.
- There may chances of microbial attack due to presence of aqueous phase.
- Short half life.
- Quickly uptake by res.
- Possible allergic reactions.
- Specialized equipment's necessary.
- Time consuming process[21,22]

Composition of liposomes

Liposomes that made up of natural lipids which are biodegradable in nature have weak immunogenicity and non-antigenic properties. These liposomes do not cause any pyrogenic reactions and exhibit little intrinsic toxicity. As cell membranes composed of phospholipids, in similar way the liposomes are formed by the polar (head) and nonpolar (tail) groups of phospholipids. The water molecules are attracted towards the polar group of phospholipids and repelled by nonpolar groups of the phospholipids. Most of the times naturally derived phospholipids are used in the liposomes preparations. Surfactant like dioleoyphosphatidylethanolamine (DOPE) is also used in liposomes preparation. The main components which constitute the liposomes are cholesterol and phospholipids[23].

Cholesterol: The liposomal bilayer is not formed by cholesterol but it gets incorporated into tail of phospholipids. Due to the amphipathic nature of cholesterol, it gets incorporated in the lipid layer in such a way that the hydroxyl group of cholesterol is towards the aqueous region and the long hydrophobic chain in aligned position to the acyl chain at the center of lipid layers. Cholesterol acts as fluidity buffer. It restricts the transformations of Trans to gauche conformations. Cholesterol incorporation increases the separation between choline head group and eliminates normal electrostatic and hydrogen bonding interactions.

Phospholipids: They constitute the major structural components of biological membranes such as the cell membrane. Phospholipids may be of natural or synthetic origin.

There are two types of phospholipids:

1. Phosphoglycerides
2. Sphingolipids

Phosphatidylcholine is the most commonly used natural phospholipids. Lecithin (amphipathic molecule) is the other name of Phosphatidylcholine. The major source of lecithin is hen's egg and vegetable oil (soya bean oil)[24]. Phosphatidylcholine is an amphipathic molecule in which exists:

- A hydrophilic polar head group phosphocholine
- A glycerol bridge
- A pair of hydrophobic acyl hydrocarbon chains

Classification of liposomes

- Liposomes are classified on the basis of
- Structural parameters
- Method of preparation
- Composition and application
- Conventional liposome
- Specialty liposome

1. Based on structural parameters
2. Based on the method of preparation
3. Based on composition and application
4. Based on composition and application.

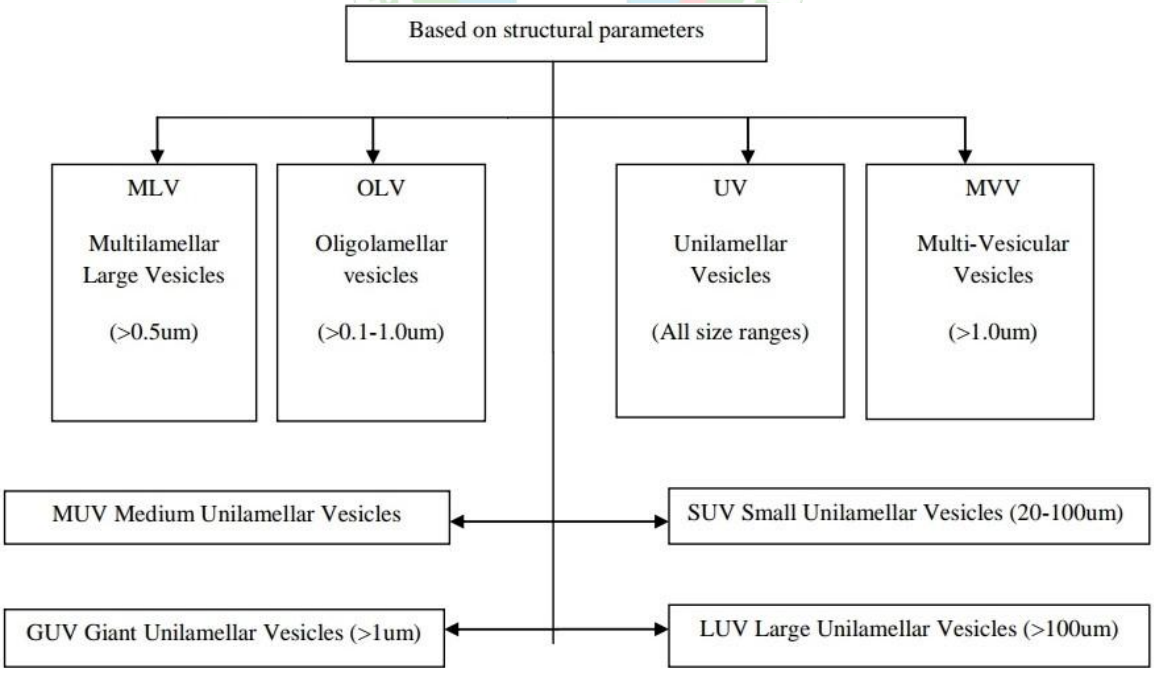

Table 1: Classification based on method of preparation

Method of preparation	Types of preparation
Single or oligo lamellar vesicle made by reverse phase evaporation method	REV
Multi lamellar vesicle made by reverse phase evaporation method	MLV-REV
Stable pluri lamellar vesicle	SPLV
Frozen and thawed multi lamellar vesicle	FATMLV
Vesicle prepared by extrusion technique	VET
Dehydration-Rehydration method	DRV

Table 2: Classification based on composition and application

Types of Liposome	Abbreviation	Composition
Conventional liposome	CL	Neutral or negatively charge phospholipids and cholesterol
Fusogenic liposome	RSVE	Reconstituted sendai virus envelops
pH sensitive liposome	-	Phospholipids such as PER or DOPE with either CHEMS or DA
Cationic liposome	-	Cationic lipid with DOPE
Long circulatory liposome	LCL	Neutral high temp. Cholesterol, and 5-10% PEG, DSP
Immuno liposome	IL	CL or LCL with attached monoclonal antibody or recognition sequences

5. Based upon Conventional Liposome
   - Stabilize natural lecithin (PC) mixtures
   - Synthetic identical, chain phospholipids
   - Glycolipids containing liposome

6. Based upon Specialty Liposome
   - Bipolar fatty acid
   - Antibody directed liposome
   - Methyl/Methylene x-linked liposome
   - Lipoprotein coated liposome
   - Carbohydrate coated liposome
   - Multiple encapsulated liposome

Mechanism of liposomes formation

Liposomes are formed after hydration of thin lipid films or lipid cakes, so masses of liquid crystalline bilayer become fluid and swell. The hydrated lipid sheets unlock during agitation and self-close to form large multi-lamellar vesicles (LMV). Self-close form prevents interaction of water with the hydrocarbon core of bilayer at the edges. The formed vesicles shape and morphology can be change after applying energy input in the form of sonic energy and mechanical energy[25].

The common feature that all bilayer forming compounds sh are is their amphilicity. They have defined polar and nonpol ar regions. In water the hydrophobic regions tend to self aggregate and the polar regions tend to be in contact with the water phase. Israelachvili and co-workers defined critical packing parameter p by

$P= v/a_0lc$

Where,

v = Molecular volume of the hydrophobic part

a_0 =Optimum surface area per molecule at the hydrocarbon water interface,

lc =Critical half thickness for the hydrocarbon region

Mechanism of transportation through liposomes

Liposome can interact with cells by four different adsorption mechanisms by specific interactions with cell-surface components, electrostatic forces, or by non-specific weak hydrophobic, which is one of the possible paths.

The second possible interaction is endocytosis by phagocytic cells of the reticuloendothelial system such as macrophages and neutrophils[26].

The third mechanism is fusion with the plasma cell membrane by insertion of the lipid bilayer of the liposome into the plasma membrane with simultaneous release of liposomal content into the cytoplasm.

And the fourth mechanism is swap of bilayer components, for instance, cholesterol, lipids, and membrane-bound molecules with components of cell membranes. It is difficult to understand what mechanism is functioning, and more than one may operate at the same time.

APPLICATIONS

Liposomes in Drug Delivery

Various liposomal systems have been proposed along with different modes of drug delivery for some of the opportunistic pathogens such as Tuberculosis, Salmonellosis, Herpes simplex virus, Leishmaniasis, Crytococcoses, and Histoplasmosis etc[27]. These systems were successfully used for delivery of different category of drugs such as anti-viral, anti-cancer, anti-inflammatory, antibiotics, anti-fungal etc. due to some unique characteristics such as increased drug solubility (amphotericin B), provide protection of molecules (DNA, RNA), enhanced intracellular uptake (anti-cancer drugs), serve as an drug depot and increase the stability of the drug.

Liposomes in Gene Delivery

Due to above characteristics, some lipid complexes have been investigated for gene delivery. DNA, RNA, Plasmid,

siRNA were successfully administered through these systems to the target organs.

Liposomes in Cosmetics and Dermatology

Due to similarity of the lipid composition and structure of human skin, liposomes are considered in cosmetics and dermatology fields. On the basis of various studies, the Trans epidermal and Trans follicular pathway are being explored for targeting of liposome encapsulated bioactive agents[28].

Liposomes in Diagnosis

It can also encapsulate various markers as well as diagnostic agents, which helps the imaging of various body organs, cells, and tissues through scanning instruments. PEGylated liposome, Stealth pH-sensitive liposomes, and paramagnetic thermosensitive Liposomes are widely used for diagnosis.

Industrial Application of Liposomes

Apart from the applications of liposomes in pharmaceutical fields, they play an important role in food industry. They act as drug, gene and cell delivery vehicles along with electrophoresis, nano-tubes, and inorganic particles. In the food industry, they protect the food products against growth of spoilage and pathogenic microorganisms by delivering food flavours, nutrient and food antimicrobials[29].

Liposomes in Cell Delivery

Recently, liposomes play an important role in tissue engineering field by using a combination of cells, engineering techniques, and suitable biochemical as well as physicochemical factors to improve and replace biological functions. They cover a broad range of applications that repair or replace portions of or whole tissues such as bone, cartilage, blood vessels, muscle etc[30].

Liposomes in Immunology

Liposomes (carrier of immunomodulators) have been used as enhancers of the immunological responses, potentiating both cytotoxic T lymphocytes and antibody production[31]. A list of antigens where liposomes have been used as Immuno adjuvants such as influenza subunit antigen, Tetanus toxoid, Bacterial poly saccharide, rabies glycoprotein, polio virus peptides, cholera toxin[32].

Liposomes as Artificial Blood Surrogates

Liposomes are investigated as artificial oxygen carrying RBC substitutes or as artificial blood surrogates. The major advantages such as prolong the half-life of encapsulated drugs and increase the oxygen transport efficiency are associated with these carrier systems.

Liposome for Respiratory Drug Delivery System

Liposomal aerosol has several advantages over ordinary aerosol.

- Sustained release
- Prevention of local irritation
- Reduced toxicity
- Improved stability in the large aqueous core

Several injectable liposomes are available in the market for lung targeting.

- Ambisomes
- Fungisomes
- Myocet

Delivery of DNA can also be done through liposome in to the lungs.

Marketed formulation of liposomes for respiratory delivery system

Table 3: Liposomes for respiratory system

Active-constituent	Effect
Insulin	Facilitated pulmonary adsorption andenhanced hypo-glycaemic effect
Catalase	Conferred resistance to pulmonary oxygen toxicity
Super oxide dismutase	Minimize toxicity to subsequent hyperoxia and improved survival
Cyclosporins	Preferentially adsorbed by lung and shows sustained release
Ricin vaccine	Improved safety profile for intra-pulmonary vaccination
Interleukin-2	The lungs facilitated bioactivity and reduce toxicity
Isoniazid and Rifampicin	Improved the effect of drugs for the tuberculosis

Liposome in Eye Disorders

- Liposomes can be used to treat disorder of both anterior and posterior segment.
- Includes dry eyes, keratitis, corneal transplant rejection, uveitis, endopthelmitis and proliferative vitro retinopathy.
- Liposome is used as vector for generic transfection and monoclonal antibody directed vehicle.
- "Verteporfin" is approved drug for the ocular delivery of liposomes.

Liposome as Vaccine Adjuvant

Firmly established as immune-adjuvant.

Liposome acts as immune-adjuvant by the following therapeutic points of view:

1. Liposomes as an immunological (vaccine) adjuvant
2. Liposomal vaccines
3. Liposomes as carrier of immuno modulation
4. Liposomes as a tool in immuno diagnosis

It acts by slowly releasing antigen or passively accumulating in to the lymph nodes.

It can be targeted in to the lymphoid with the help of phosphotidyl serine.

Table 4: Antigens as liposomal preparation and their application

Antigens as Liposomal Preparation	Applications
Rabies glycoprotein	Interleukin-2 enhancement
Cholera toxin	Enhanced Ab* level
Diphtheria toxoid	Superior immunoadjuvant
Herpes simplex virus	Enhanced Ab level
Hepatitis B virus	Higher Ab response
Bacterial polysaccharides	Superior immunoadjuvant
Tetanus toxoid	Increased Ab titre
Influenza subunit antigen	Intranasal, protects animal from virus
Carbohydrate antigen	Increased Ab titre in salivary gland

Liposome for brain targeting

- Liposome with a small diameter (100nm) as well as large diameter undergoes free diffusion through the Blood Brain Barrier (BBB).
- SUVs couples with the brain drug transport vector to cross the BBB by the adsorptive mediated transcytosis.
- Cationic liposomes successfully undergo absorptive mediated endocytosis in to cells.
- Addition of the sulphatide (a sulphur ester of galactocerebroside) to liposome composition increases ability to cross BBB.
- Wang et al. Reported that mannose coated liposomes reach brain tissue and the mannose coat assist transport of loaded drug through BBB.
- Polysorbate 85 recognize that it enhance the significance in to the brain. eg.Amitriptylline

Liposome as Anti-Infective Agents

Intracellular pathogen like protozoal, bacterial and fungal remove by targeting the liposome to their residence inside the body.

Table 5: Liposomal preparation for infective disease

Active Constituents	Application
Active targeting approach	
Pentamidin	Leishmaniasis
Anti sense oligonucleotide	Leishmaniasis
Anamycin	Leishmaniasis
Asiaticoside	Tuberculosis and Leprosy
Rifampicin	Tuberculosis
Passive targeting approach	
Amphotericin B	Meningitis, Leishmaniasis, Candidiasis
Praziquantel	Macrophage activation
Sparfloxacin	M. avium, M.Intracellularie complex
Gentamycin	Staphylococcal pneumonias

Liposome in Tumor therapy

- The long term therapy leads to several toxic side effects.
- The liposomal therapy for tumor targeting shows least side effect.
- Small and stable liposome passively targets the tissue and extra vasate in tissue with long circulation.
- Doxil is the liposomal formulation of doxorubicin (stealth liposome)
- Liposome which is prepared by several means. Caelyx and myocet are the liposomal formulations of doxorubicin.
- Caelyx is used for treatment of metastatic ovarian cancer but noe in advanced breast cancer.
- Myocet is approved for metastatic breast cancer.

Various Intravenous Liposomal Antibiotics / Anti- Neoplastics

Table 6: Liposomal antibiotics

Preparation	Drug	Targeted Site
Liposome (Doxil)	Doxorubicin	Kaposi' sarcoma
Liposome (EVACT™)	Doxorubicin	Refractory tumor, Metastatic breast cancer
Liposome (DaunoXome)	Daunosome	Advanced Kaposi' sarcoma, small cell lung cancer, leukaemia and solid tumor
Liposome	Nystatin	Systemic fungal infection
Liposome	Anamycin	Kaposi' sarcoma, Refractory breast cancer
Liposome (VincaXome)	Vincristine	Solid tumor
Liposome (Mikasome)	Amikacin	Serious bacterial infection

Lymphatic targeting with liposome

- Because subcutaneous administration of liposome results in their uptake by draining lymphatic capillaries at the injection site.
- Active capture of liposomes by macrophages in regional lymph nodes.
- Liposome uptake by lymph nodes might be increased by using biotin bearing liposome for preliminary injection.
- Liposome has been use for lymphatic delivery of methotrexate and magnetic resonance imaging (MRI) with gadolinium (Gd) loaded liposome[33].

Table 7: Therapeutic application of liposome

Drug	Route of administration	Application	Targeted disease
Amphotericin B	Oral delivery	Ergosterol membrane	Mycotic infection
Insulin	Oral, ocular, pulmonary and transdermal	Decrease glucose level	Diabetic mellitus
Ketoprofen	Ocular delivery	Cyclooxygenase enzyme inhibitor	Pain muscle condition
Pentoxyfyllin	Pulmonary delivery	Phosphodiesterase	Asthama
Tobramycin	Pulmonary delivery	Protein synthesis inhibitor	Pseudomonas infection, aeroginosa
Salbutamol	Pulmonary delivery	B_2-adrenoceptor antagonist	Asthama
Cytarabin	Pulmonary delivery	DNA polymerase inhibition	Acute leukaemia
Benzocaine	Transdermal	Inhibition of nerve impulse from sensory nerves	Ulcer on mucous surface with pain
Ketoconazole	Transdermal	Inhibit ergosterol membrane	Candida albicans
Levanogesterol	Transdermal	Rhamnose receptor	Skin disorder
Hydroxyzine	Transdermal	H_1-receptor antagonist	Urtecaria, allergic skin disorder
Ibuprofen	Oral delivery	Chaemoceptor, free ending	Rheumatoid arthritis

Table 8: Marketed products of liposome

Name	Trade name	Company	Indication
Liposomal amphotericin B	Abeket	Enzon	Fungal infections
Liposomal amphotericin B	Ambisome	Gilead Sciences	Fungal and protozoal infection
Liposomal cytarabine	Depocyt	Pacira(formerly skyepharma)	Malignant lymphomatous meningitis
Liposomal daunorubicin	DaunoXome	Gilead Sciences	HIV-related kaposi's sarcoma
Liposomal doxorubicin	Myocet	Zeneus	Combination therapy with cyclophosphamide in metastatic breast cancer
Liposomal IRIV vaccine	Epaxal	Berna Biotech	Hepatitis A
Liposomal IRIV vaccine	Inflexal V	Berna Biotech	Influenza
Liposomal morphine	DepoDur	Skyepharma, Endo	Postsurgical analgesia
Liposomal verteporfin	Visudyne	QLT, Novartis	Age-related macular degeneration, pathologic myopia, ocular histoplasmosis
Liposome-PEG doxorubicin	Dox1/Carlyx	Ortho Biotech, Schering-plough	HIV-related kaposi's sarcoma, metastatic breast cancer, metastatic ovarian cancer
Micellular estradiol	Estrasorb	Novavax	Menopausal therapy

LIPOSOMAL DELIVERY: FUTURE CHALLENGES

Threemajor problems such as reticulo-endothelial system uptake, extensive production and instability of phospholipids that pose as a problem in their marketable development. Due to these problems or challenges, only few products such as Daunoxome, Ambisome, Doxil,

Epaxel etc. have come up with the stage of commercial production[34].

Stability

Liposomes pose physical as well as chemical instability. They cannot be stored for a longer period due to oxidation and/or hydrolysis of phospholipid used for their production.

Large Scale Production

Various steps such as preparation of thin lipid film, sonication, solvent evaporation etc. are used for the fabrication of liposomes. These steps are very difficult to perform at laboratory level at large scale, costly and difficult to control of their production as per the regulatory norms[35-36].

Reticulo-endothelial System Uptake

Liposomes are accordingly endocytosed by mononuclear phagocyte system (MPS), but it's include site specific drug delivery by using ligands which mainly expressed on the surface of liposomes in order to bind to receptors overexpressed on the diseased cells. So, search of liposomes hasdiscovered that could avoid quick curiosity by the MPS taking place and rare lipid compositions that extended liposome blood circulation periods.

CONCLUSION AND FUTURE PERSPECTIVES

This article reviewed the possible applications of liposomes and discussed, in brief, some problems associated with formulation and development. From the above study, we can conclude that the above nano-carrier system has an immense opportunity for the designing of a novel, low-dose and effective treatment systems to control various diseases. An encouraging sign is the increasing number of clinical trials involving liposome and lipid-based products. Several companies are actively engaged in expansion and evaluation of liposome products for use against several diseases. Liposomes have been realized as extremely useful carrier systems and tools in various scientific domains such as biophysics, biochemistry, physics, chemistry, physical chemistry, colloidal science, mathematics, biology, ecology, pharmacology and pharmaceutical sciences. The uses of liposomes in the delivery of drugs, genes and cell to the target sites are promising and may serve as a handle for focus of future research.

LIST OF ABBREVIATIONS

CMC	Critical micellar concentration
RNA	Ribonucleic acid
MLV	Multilamellar vesicles
LUV	Large unilamellar vesicles
PC	Phosphatidyl choline
LMV	Large multi lamellar vesicles
Ab	Antibody
SUV	Small unilamellar vesicles
DNA	Deoxyribonucleic acid
DOPE	Dioleoyphosphatidyl ethanolamine
OLV	Oligo lamellar vesicles
UV	Unilamellar vesicles
MVV	Multi vesicular vesicles
MUV	Medium unilamellar vesicles
GUV	Giant unilamellar vesicles
CL	Conventional liposome
RSVE	Reconstituted sendai virus envelops
IL	Immuno liposome
LCL	Long circulatory liposome
LMV	Large multi lamellar vesicles
LAL	Limulus amebocyte lysate
BBB	Blood brain barrier

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