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An Overall Review on Liposomes and Its Drug Delivery Systems

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ABSTRACT: Liposomes are sphere shaped vesicles consisting of one or more phospholipid layers. These having sizes ranges from 10-9m are called Nano-liposomes.Liposomes characterize an advanced technology to deliver active molecules to the site of action, and at present, several formulations are in clinical use.These are the most common and well investigated nano-carriers for targeted drug delivery. Liposomal drug delivery targets tissue with or without expression of target recognition molecules on lipid membrane. Liposomes are the leading drug delivery systems for the systemic(intravenous) administration of drugs. Agents that prolong the circulation lifetime of liposomes, enhance the delivery of liposomal drugs to specific target cells, or enhance the ability of liposomes to deliver drugs intracellular can be incorporated to further increase the therapeutic activity.Drugs encapsulated in liposomes can be targeted actively and passively in which it reduces target effects and improves efficacy.Encapsulation within liposomes protects compounds from early inactivation,degradation and dilution in the circulation. Liposomes are generally considered to be pharmacologically inactive with minimal toxicity,as they tend to be composed of natural phospholipids. These advances have led to numerous clinical trials in such diverse areas as the delivery of anti-cancer.

KEY WORDS: Liposomes,Nanoliposomes, Drug delivery, encapsulation of drug, multilamellar, Immunogenicity.

I. INTRODUCTION:

Liposomes are described by Alec Bangham in 1961 in England.These are spherical vesicles with a phospholipid bilayer which are separated by water or aqueous buffer compartments with a diameter ranging from 25 nm to 10000 nm. These are composed of phospholipids,especially phosphatidylcholine. Liposomes can entrap both hydrophilic and hydrophobic drugs and avoids decomposition of entrapped combinations. These liposomes are extensively used as carriers for numerous molecules in cosmetics and pharmaceutical industries. The use of liposome encapsulation is also studied by food and farming industries to grow delivery systems that can entrap some unstable compounds like bioactive elements, antioxidants, antimicrobials and flavours[1-3].These are classified based on the method of preparation and applications. Many methods have been reported for the preparation of liposomes. In liposomes, drug release rates have important implication for the therapeutic activities. Drug entrapped in liposomes becomes bioavailable only when it is released[4-5]. Liposomes are with great variety of molecules like small drug molecules, nucleotides, proteins and even plasmids[6]. Lipofection is type of process in which liposomes are used as transformation or transfection of DNA into a host cell.Due to these types of unique properties liposomes are used for drug delivery.

Liposomes act within and outside the body by several mechanisms like:

1.Liposomes attaches to cellular membrane and releases their contents into the cell by fusing with them.

2. In some phagocytic cells, phospholipid walls of liposomes are taken up by organelles called lysosomes and active pharmaceutical ingredients are released.

Liposomes had a unique opportunity to deliver the drugs into cells by fusion or by endocytosis mechanism, irrespective of drugs solubility it can be entrapped into liposomes. Liposomal drug delivery system has many developments like liposomal carriers for conventional drugs, immunological adjuvants and vaccines, preclinical and clinical trials.Liposomes

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have been considered as excellent models of cell membranes and have been employed as potent drug carriers in which various materials such as drugs,proteins,enzymes,toxins,antigens and nucleotides are encapsulated. These liposomal encapsulation can alter the spatial and temporal distribution of the encapsulated drug molecules in the body,which may significantly reduce unwanted toxic side effects and increase the efficacy of treatment.Liposomes has many advantages and disadvantages in case of drug delivery. Some liposomes can also applied as creams, gels and tinctures. These liposomal drug delivery also has a beneficial use especially when an existing formulation is not satisfactory and reformulation in liposomes offers clear benefits with respect to target ability,therapeutic efficacy and safety compared to the existing formulations.[7]

LIPOSOMES:

Liposomes are vesicles in which an aqueous volume is entirely enclosed by a membrane composed of lipid molecules usually phospholipids and these are found in cell membranes. The liposome can be used as a drug delivery vehicle for administration of nutrients are easily controlled. Lecithin(mixture of phospholipids) and cholesterol are the main components of liposomes. These liposomes can be prepared by disrupting biological membranes.Liposomes are biodegradable and essentially non-toxic vehicles[8].These liposomes can encapsulate both hydrophilic and hydrophobic materials, and are used as drug carriers in drug delivery systems. Liposomes with 50-150 nm range in diameter of unilamellar are usually preferred in drug delivery applications. Larger liposomes are rapidly removed from blood circulation.Liposomes involves in various cell processes and they destroy many diseases.

TYPES OF LIPOSOMES:

Based on structure,liposomes are two types, they are;

Unilamellarliposomes: Unilamellar vesicle has single phospholipid bilayer sphere enclosing aqueous solution.

Multilamellarliposomes: Multilamellar vesicles have onion structure.

A number of or bunch of unilamellar vesicles will form one inside and the other in diminishing size, thereby creating a multilamellar structure of concentric phospholipid spheres which are separated by layers of water.

Types of liposomes used of different applications:

Stealth liposomes	selective targeting to pathological areas
Conventional liposomes	Targeted delivery to macrophages and in vaccines
pH sensitive liposomes	Targeting tumours and in endocytosis
Immuno liposomes	Receptor mediated endocytosis
Temperature sensitive liposomes	Site specific delivery of solid tumours
Magnetic liposomes	targeting antibodies to brain
Cationic liposomes	Gene delivery

CLASSIFICATION OF LIPOSOMES

Liposomes are classified based on

1.Structure:

a) Unilamellar vesicle: Unilamellar diameter ranges in all sizes and it contains one lipid bilayer.
b) Small unilamellar: Small unilamellar diameter size ranges in 20-100nm and it contains one lipid bilayer.
c) Medium unilamellarvesicle: Medium unilamellar vesicle diameter ranges more than 100 nm and it contains one lipid bilayer.
d) Large unilamell arvesicle: Large unilamell arvesicle diameter ranges more than 100 nm and it contains one lipid bilayer.
e) Multilamellarvesicle: Multi lamellar vesicle diameter ranges more than 0.5 and it contains 5-25 lipid bilayer.

2. Method of preparation:

a) Single or oligolamellar vesicle type andmultilamellar vesicle type of liposomes are formed by reverse phase evaporation method.
b) Vesicles are prepared by extrusion technique.
c) Multilamellar vesicle type of liposomes are also prepared by frozen and thawed method.

Liposomes are also prepared by some general methods like drug loading capacity and also by dispersion method. Mechanical methods, replacement of organic solvent and fusion of prepared vesicle or size transformation are the

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different strategies were also used for this preparation of liposomes.

3. Composition and Application:

a) Composition of PH sensitive liposomes are phospholipids such as PER or DOPE with either CHEMS or OA.
b) Composition of conventional liposomes are neutral or negatively charge phospholipids and cholesterol.
c) Composition of long circulatory liposomes are neutral high temp, cholesterol, and 5-10% PEG, DSP.
d) Composition of cationic liposomes are cationic lipid with DOPE.
e) Composition of Immnuno liposomes are CL or LCL with attached recognitionsequences or monoclonal antibody.

Based upon specialty liposomes

1. Multiple encapsulated liposome.
2. Lipoprotein coated liposome.
3. Carbohydrate coated liposome.
4. Bipolar fatty acid.
5. Antibody directed liposome.

Based upon conventional liposomes

1. Glycolipids containing liposome.
2. Synthetic identical,chain phospholipids.
3. Stabilize natural lecithin (PC) mixtures.

Mechanism Of Transportation Through Liposome:

Liposomes interact with the cells by four different mechanisms (Thomas and joseph, 2002).

1. Endocytosis occurs by phagocytic cells of reticuloendothelial system (such as neutrophils and macrophages).
2. Without any association of liposome contents, liposomal lipids transfer to cellular or subcellular membranes, or vice versa.
3. By insertion of lipid bilayer of liposome into the plasma membrane by fusion with plasma cell membrane, releases simultaneously liposomal content into the cytoplasm.
4. Adsorption of cell surface occurs by specific interactions with cell surface components or by electrostatic forces or by non-specific weak hydrophobic forces.

PRODUCTION OF LIPOSOMES FOR CONVENTIONAL DRUG DELIVERY:

The liposome technology has shown the ability to produce well defined liposomes which are composed of a wide variety of lipids with different physical and chemical properties,having high drug-trapping efficiencies and having narrow size distribution,averaging less than 100nm in diameter.These properties significantly affects the stability and pharmacokinetics of liposomes[9].Many procedures have been established to produce well-defined liposomes[10-11].For this a process called as extrusion, is done, where liposomes are forced through filters with well-defined pore sizes under sonication,moderate pressures,reversed-phase evaporation and detergent based procedures. While maintaining the integrity of liposome structure another significant advance has come from ability to entrap drugs in liposomes with the high efficiencies.

Drug loading can be achieved either by passively or actively (passively- the drug is encapsulated during liposome formation; actively-after liposome formation).During vesicle formation, Hydrophobic drugs can be directly incorporated into liposomes and extent of uptake and retention is governed by drug-lipid interactions.Depending on the solubility of the drug in liposome membrane trapping efficiencies are 100 % achievable.Passive encapsulation of water-soluble drugs is to impart an amphipathic nature to the drugs by complexing or conjugating the drugs to lipids[12-13]. Alternatively, some water-soluble drugs which have ionizable amine functions can be actively entrapped by employing PH gradients[14], this results in trapping efficiencies approaching 100%.

LIPOSOMAL DRUG DELIVERY SYSTEM:

Liposomes have great potentials of effective delivery of drugs to site of action and of controlling the release of these drugs at a predetermined rate. Liposomes are lipotropic liquid crystals, which are composed of relatively biodegradable materials and biocompatible and consists of an aqueous core entrapped by one or more bilayers of natural or/ and synthetic lipids.An opportunity has been provided to enhance the therapeutic indices of various agents mainly through alternation of bio distribution by reformulation of drugs.They are versatile drug carriers, in the presence of biological fluids,which can be used to control retention of entrapped drugs ,controlled vesicle residence in the systemic circulation or other components in the body and enhances vesicle uptake by target cells[15].Natural lipid liposomes are biodegradable, weakly immunogenic and biologically inert[16],with limited intrinsic toxicity and produce no pyrogenic reactions or antigenic reactions[17].Therefore, drugs

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which are encapsulated in liposomes are expected to be transported with minimum side effects and without rapid degradation to the recipients.

Moreover, efforts have been made to evaluate the specificity of the drug carriers to the target cells or compartments within the cells and organs[18].when compared to other drug carriers such as micro emulsions and nanoparticles,liposomes are well suited for assessing their targetable properties due of ease of modifying their surface[19,20].To achieve targetable properties, many approaches have been attempted including coating of liposomes with heat aggregated immunoglobulins M (IgM)[21],noncovalent association of cell specific antibodies with liposomes [22],covalent attachment of poly and monoclonal antibodies to the liposomes[23-31],natural[32-34] and synthetic[35-39] glycolipid containing liposomes and glycoprotein bearing liposomes[40].The entrapped compounds in liposomes are protected from action of external media, particularly inhibitors and enzymes[41]. Hence liposomes afford a unique opportunity to deliver the drugs into the cells by endocytosis mechanism or by fusion and particularly any drug can be entrapped into liposomes irrespective of its solubility.

Liposome in encapsulation of Drug:

There are several advantages in encapsulation of drugs in liposomes, as it represents a new drug delivery system that appears to offer important therapeutic advantages over existing methods of drug delivery (Wong et al., 1997).Bio distribution and drug elimination characters (pharmacokinetics) undergo some changes due to stable encapsulation of drugs in liposomes. Macrophage functions are dramatically enhanced by liposome-encapsulated quinolones and specifically liposome encapsulated ciprofloxacin,induces NO production and augments the production of cytokines,rendering composition an immunotherapeutic agent immunoprophylactic agent unique clinical potential.Liposome-encapsulated ciprofloxacin and other quinolones could be extremely useful in anticancer,antimicrobial and AIDS therapies. In such cases, patient immunological status if often suppressed or compromised, making them susceptible to microbial infections and to development of tumor growth.NO and cytokine production has primary importance as they protect against microbial infections.

Liposomal encapsulated drugs reduces the volume of distribution and decreases toxic side effects in healthy tissues.For example free drugs which are injected into the bloodstream usually have a large volume of distribution and as a consequence exhibit significant toxicity for health tissues .when the drug is bioavailable (released from the liposomes), it results in increased efficacy this is due to the increased circulation lifetimes result in higher levels of accumulation at disease sites as compared to free drug.In pain management liposome- encapsulated analgesic drugs are also used.The development of liposomal drugs with the clinical utility depends on the development of techniques,which allowed the efficient accumulation of drugs into liposomes and rapid generation of homogenous small liposomes. Encapsulation efficiency of liposomes is trapped volume and is usually expressed in µ1/mg of total lipids.

Advantages of Liposome:

1. Liposomes reduce the toxicity of the encapsulated agent (Amphotericin B, Taxol).
2. Liposomes help reduce the exposure of sensitive tissues to toxic drugs.
3. Liposomes increased efficacy and therapeutic index of drug (Actinomycin –D).
4. Liposome increased stability via encapsulation.
5. Liposomes are non-toxic, biocompatible, flexible, non-immunogenic for systemic and non-systemic administrations and completely biodegradable.

Disadvantages of Liposome:

1. Production cost is high.
2. Short half-life.
3. Low solubility.
4. In some cases phospholipids undergoes oxidation and hydrolysis like reaction.
5. Fusion of encapsulated drug/molecules and leakage.

Applications of Liposomes:

Liposomal applications in pharmacology and medicine can be divided into therapeutically and diagnostically, as these liposomes are containing various drugs, and their use as a tool, a model in the basic studies of cell interactions,recognition processes and mode of action of certain substances[42].

1. For new biotechnologyproducts, liposomal advances are leading to new applications, for example clones genes, antisense oligonucleotides and recombinant proteins.

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2. To cause liposomal components to be associated with target cells, liposomes interact with cells in many ways[43].
3. In the treatment of cancer and systemic fungal infections had the most advancedapplications.
4. Many liposomal drug formulations are used in preclinical development and also in clinical trials.
5. Liposomes are used as models for artificial cells and also designed to delivers drugs in other ways.
6. **Tumortherapy:** For medical applications as drug carriers the liposomes can be injected intravenously.
7. **Liposomes as vaccine carriers:** Liposomes potentiate both cell mediated and humoral immunity.
8. **In gene delivery:** Lipid based systems, polymers,peptides and liposomes are non-viral gene delivery vehicles.
9. **Liposomes as artificial blood surrogates**: liposome encapsulated hemoglobin products are being investigated as artificial RBC's.
10. **Liposomes as radiopharmaceutical and radio diagnosticcarriers**: These include liver and spleen imaging,lymphatic imaging, tumor imaging, blood pool imaging and infection sites.
11. **Cosmetics and dermatology:**Liposomes carrying skin-care material is an excellent addition to the daily skin-care programs.
12. When these liposomes combines with essential oil provide an effective nourishing treatment that penetrates deeply into the skin.

II. CONCLUSION:

Pharmaceutical applications of liposomes are used in broad range. Liposomal drug delivery has gained considerable clinical acceptance. Liposomes can be actively targeted by using several methods such as antibodies, carbohydrates, peptides.Many liposome based drug delivery systems is currently approved by FDA. Liposomes showing particular promise as intracellular delivery systems for anti-sense molecules, proteins, DNA and ribosomes. Compared with complements liposomes exhibit reduced toxicities and retains enhanced efficacy. Medication's bioavailability has improved by this liposome encapsulation, which can reduce dosing and extend treatment effect. Liposomal encapsulation alters drug's absorption, distribution, metabolism and excretion, it can potentially address many of current problems with controlled drug delivery. Glycolipid or glycoprotein cell surface components that play a role in interaction, cell-cell recognition and adhesion are used to overcome the limitation of liposomal drug targeting. Liposomal drug delivery systems have played a significant role to improve therapeutics by reformulation of potent drugs.

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