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REVIEW ON lIPOSOMES AS A NOVEL DRUG DELIVERY SYSTEM: PHARMACEUTICAL APPLICATION.

Jagtap Pratik B,

Ms. Deokar K. A, Mr. Gadade A.B.

Gangai pharmacy college Kada

ABSTRACT:

Liposome is a micro particulate colloidal vesicle, in which aqueous medium is surrounded by single or multiple concentric layers of phospholipids. Both hydrophilic & hydrophobic drug can be incorporated, water soluble drug being trapped in aqueous core and fat soluble drug in phospholipids. It offers controlled release, targeted drug delivery thus enhanced therapeutic efficacy and reduced dosing frequency. Several liposomes based drug formulation are approved for clinical use and many are under extensive investigation. Therapeutically, these are used as carrier for drugs, viruses, bacteria, antigen, peptides (antibiotic), vaccines, genes and diagnostic agents. This review discusses about the method of production and extensive therapeutic potential of liposomes as carriers for targeted and controlled delivery.

KEYWORDS:

Liposomes; Novel drug; Controlled release; Currier; Drug targeting.

INTRRODUCTION:

Liposomes were spherical shaped concentric vesicles derived from two Greek words lipos means fat and soma means body1. Liposome were first made by Bangham et al in 1961, it was an accidental discovery in which he scattered the phosphatidyl choline molecule in water, during this he found that the molecule was forming a closed bilayer structure having an aqueous phase which were entrapped by a lipid bilayer2. Liposome very useful because act as a carrier for a variety of drugs, having a potential therapeutic action or other properties. Liposome is colloidal carriers, having a size range of 0.01–5.0μm in diameter. Drug encapsulated by liposome achieve therapeutic level for long duration as drug must first be release from liposome before metabolism and excretion3. They are small

artificial vesicles of spherical shape that can be created from cholesterol and natural non-toxic phospholipids. Due to their size and hydrophobic and hydrophilic character (besides biocompatibility), liposome's are promising systems for drug delivery4. There is a unique ability of liposomes to entrap drugs of both aqueous and the lipid phase and it makes them attractive drug delivery systems for hydrophilic and hydrophobic drugs5. Liposomes are the novel drug delivery system that aims to deliver the drug directly to the place of action. They have potential to accommodate both hydrophilic and lipophilic compounds to protect the drug from degradation and release the active ingredients in a controlled manner6. It has been found that glycerol is the backbone of a molecule that's why phospholipid containing glycerol were found to be an essential component of liposomal formulation and it represents 505 of lipid weight7.

A liposome is a tiny bubble (vesicle), with a membrane composed of a phospholipid bilayer. Membranes are usually made of phospholipids like phosphatidylethanolamine and phosphatidylcholine. Phospholipids are amphiphilic with its polar head as hydrophilic and hydrocarbon tail as hydrophobic.

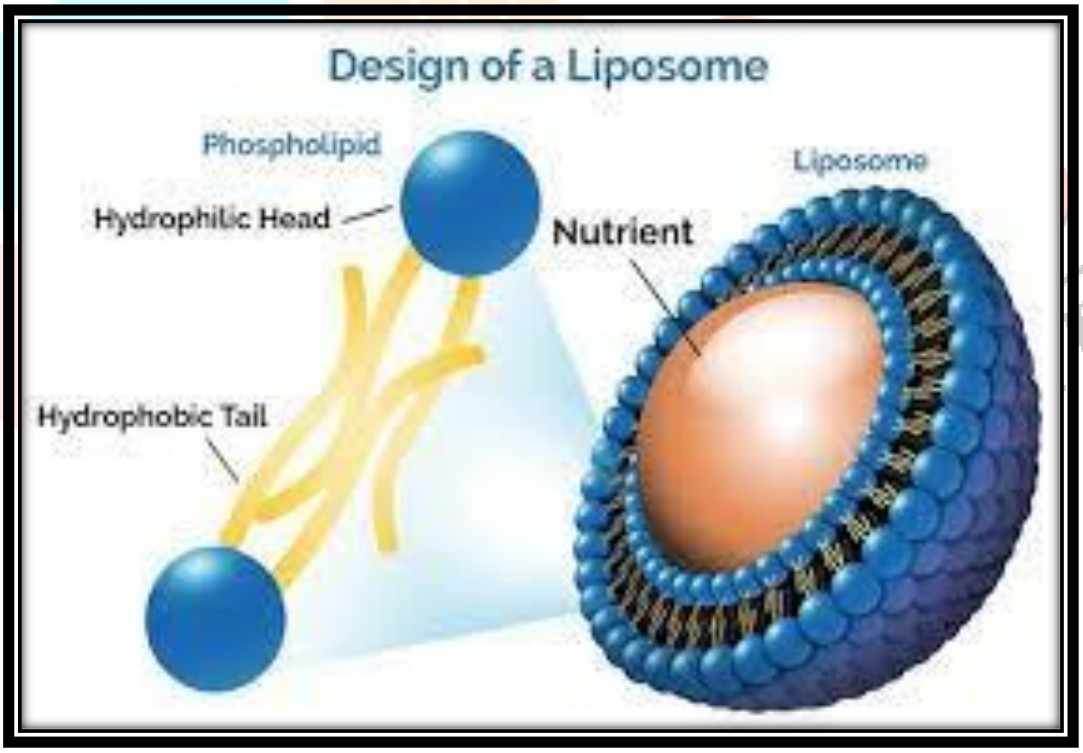

Fig1.Desing of Liposome

ADVANTAGE:

1. They offer targeted drug delivery.
2. They are biocompatible, biodegradable and biologically inert.
3. They are nonantigenic, nonpyrogenic and nontoxic.
4. They can encapsulate both water soluble and water insoluble drugs.
5. Drug toxicity is removed as other tissues and cells are protected.

6. Cellular uptake of drug is enhanced.

7. Size can be varied to incorporate smaller or larger drug molecules.

Disadvantages:

1. Liposomes are less stable.

2. They are rapidly removed by cells of reticuloendothelial system (RES) from blood after iv injection.

3. Drug release is slow and influenced by phagocytes

4. Low solubility

5. Less stable

6. Prouction cost is high

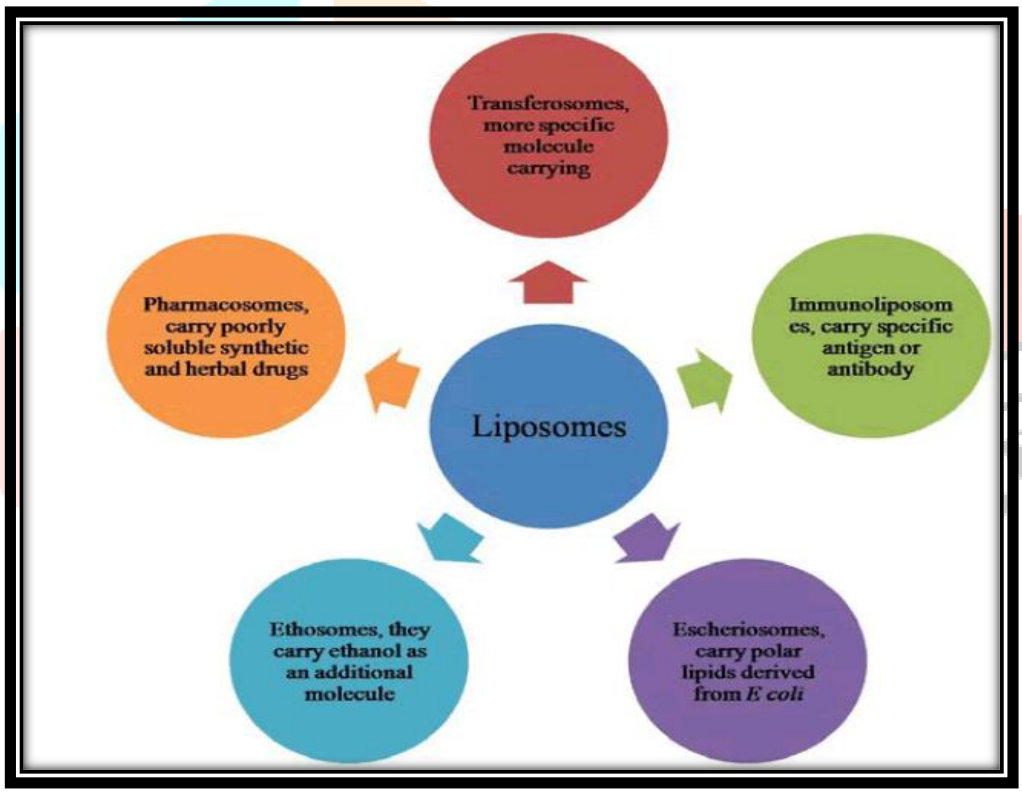

Fig 2. Different type of Liposomes

CLASSIFICATION OF LIPOSOMES:

Liposomes are effective carriers for drug delivery, including small and large molecules (proteins, peptides, and DNA). Generally, we can classify liposomes based on the preparation method, the number, and size of vesicle bilayers, *etc*

Classification based on Structure:

According to the size and number of bilayer membranes (lamellarity) forming vesicles, liposomes can be divided into the following categories (1)

- Small unilamellar vesicles (SUV): 20-100 nm.
- Large unilamellar vesicles (LUV): >100 nm.
- Giant unilamellar vesicles (GULV): >1000 nm.
- Oligolamellar vesicles (OLV): 100-1000 nm.
- Multilamellar large vesicles (MLV): >500 nm.
- Multivesicular vesicles: >1000 nm. (3)

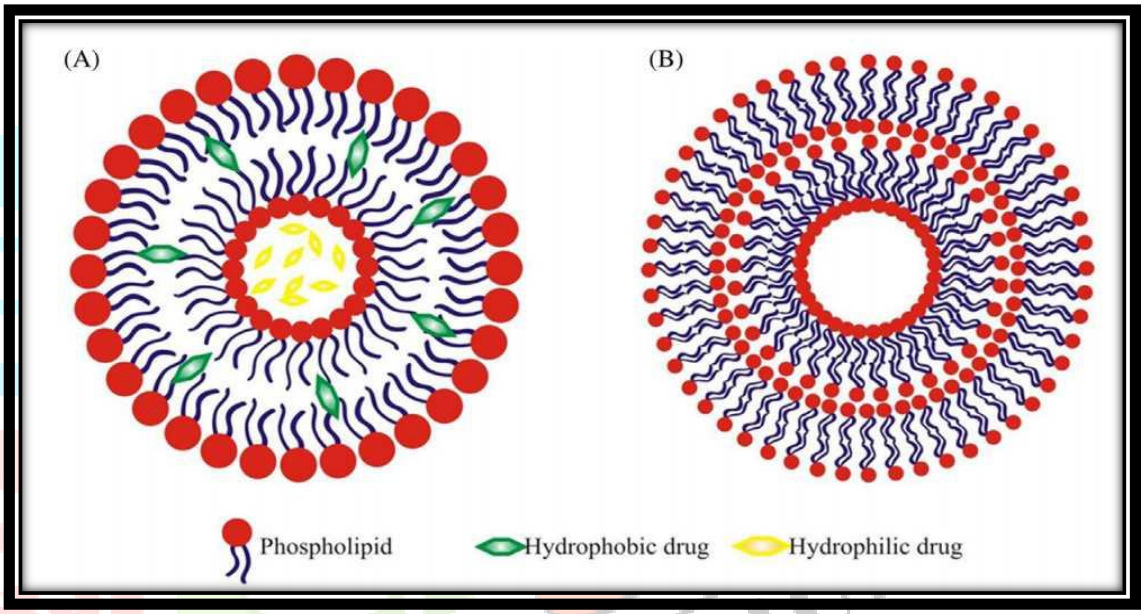

Fig.2 The schematic representation of (A) unilamellar and (B) multilamellar liposome vesicles.

Classification based on Composition and Application A:

Liposomes can be divided into several different types according to their composition and application, including(19)

- **Conventional liposomes:**

Conventional liposomes are the first generation of liposomes. They are lipid bilayer molecules surrounding the aqueous chamber and are the basis of all subsequent liposomes. (25)

- **Immunoliposomes:**

Immunoliposomes are vesicles specially designed for active targeting of the drug substances inside the body. (26)

- **Long circulating liposomes:**

The surface modification or PEG modification of liposomes is called PEGylation of liposomes, and the modified liposomes are called long circulating liposomes or stealth liposomes. Compared with conventional liposomes, PEG liposomes can avoid phagocytosis and circulate for a long time in systemic circulation. (24)

- **Cationic liposomes:**

Cationic liposomes can be prepared by adding cationic phospholipid into bilayer membrane. This allows high rates of DNA incorporation, and for this reason, such liposomes may be more suitable for gene and antisense therapy. (18)

- **Stimuli-responsive:**

Liposomes can be easily functionalized through the introduction of functional materials, such as stimulus-response materials. Their structure, configuration, and other properties can be changed under certain *in vivo* or *in vitro* stimulation, such as the change of heat, light, magnetism, and pH value. (9)

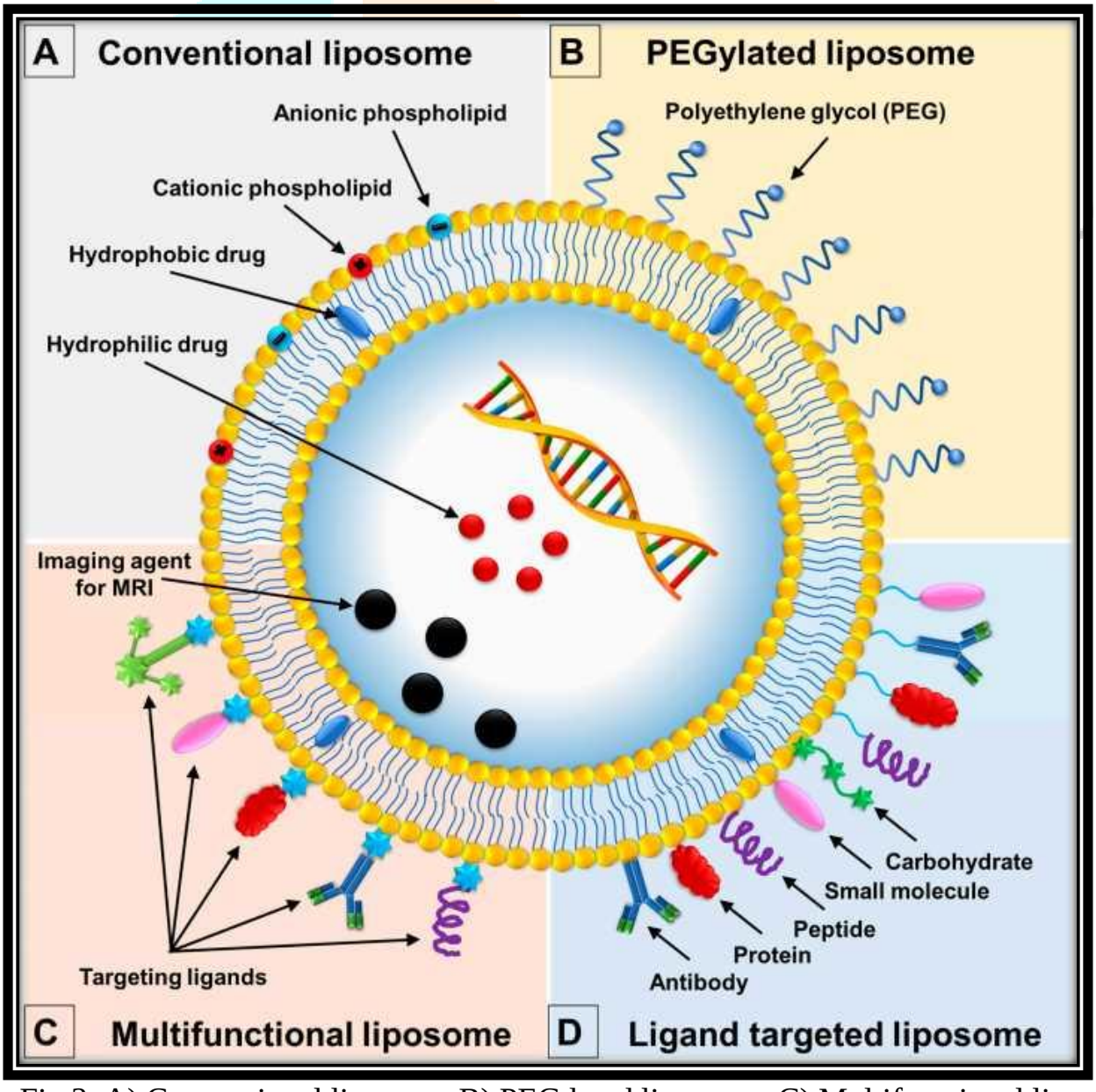

Fig 3. A) Conventional liposome,B) PEG lated liposome ,C) Multifunctional liposome , D) Ligand targeted liposome.

Classification based on Preparation Method:

In addition to the above two classification methods, liposomes will also be classified according to their preparation methods. This classification depends on using the organic solvents, obtaining different lamellarity of liposomes, changing the size and applications of liposomes.(17)

REV SUVs/OLVs/MLVs: made by reverse-phase evaporation method

SPLV: stable plurilamellar vesicle

DRV: made by dehydrated rehydrated method

VET: vesicles prepared by extrusion technique

FATMLVs: frozen and thawed MLVs.(20)

Methods of preparation of liposomes :

Thin- film hydration method/Hand shaking method This method was developed by Bangham et al, for the preparation of multilamellar vesicles. Briefly, phospholipids are dissolved in a mixture of organic solvents (chloroform and methanol). The lipids are deposited as stacks of film from the organic solvents on the wall of round bottom flask by the process of rotary evaporation under reduced pressure. Upon hydration of lipids by addition of aqueous buffer containing the drugs, lipids tend to swell and peel off from the walls of round bottom flask results in the formation of multilamellar vesicle. A mechanical energy is required to cause swelling of lipids and dispersion of lipids film by simple hand shaking technique. Alternatively, exposing lipid film into a water saturated nitrogen for a stipulated period of time usually 15 minutes also results in the swelling of lipids without the use of agitation. (6)

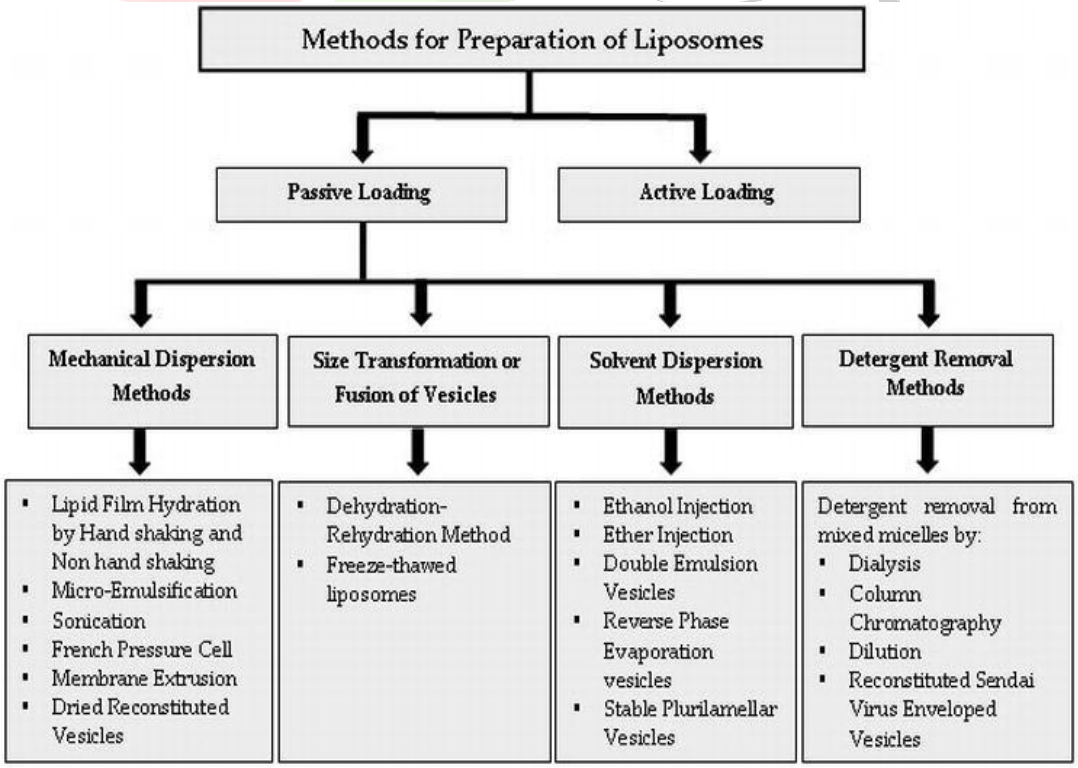

Table 1. Method for Preparation of Liposome

MECHANISM OF ACTION OF LIPOSOMES:

- **Liposome performs their action by four different mechanism. They are as follows:**

1. Endoytosis – This take place by phagocytic cells of reticuloendothelial system such as neutrophils. (23)

2. Adsorption – It occurs to the cell surface by nonspecific electrostatic forces or by interaction with cell surface components. (21)

3. Fusion- It occurs by the insertion of liposomal bilayer into plasma membrane with continuous release of liposomal content into the cytoplasm. (22)

4. Lipid exchange - In this transfer of liposomal lipids to the cellular membrane without association of liposomal contents.(16)

EVALUATIONS OF LIPOSOMES :

1) Vesicle shape and lamellarity: The shape of the vesicles were studied by using electron microscope.(14)

2) Particle size and distribution: The size analysed by an analyzer based on laser diffraction theory focused with minimum power of 5MW31.(15)

3) Entrapment Efficiency : It determines amount and rate of entrapment of water soluble agents in aqueous compartment of liposomes.(13)

4) Trapped Volume : It is an important parameter related to liposomes .It is aqueous entrapped volume per quantity of lipids. This can vary from 0.5 to 30 microlitre/micromol32.

5) In vitro drug release : This can be carried by using Franz Diffusion cell which has a diameter of 25 mm .It contains reservoir compartment of 22 ml which was filled with buffer which contains 20%v/v methanol to maintain sink condition.(12)

MARKETED FORMULATIONS OF LIPOSOMES:

In 1995, Doxil (PEGylated liposome-encapsulate doxorubicin) became the first liposome drug delivery system approved for human use by the US FDA. There was list of marketed formulations of liposomes.

Fig. 4 Marketed Liposomes

Sr.No.	Name of Drug	Name of Product	Current status
1.	Doxorubicin	Lipodox	Marketed
2.	Doxorubicin	Myocet	Marketed
3.	Doxorubicin	Doxil/Caelyx	Marketed
4.	Mitoxantrone	LEM-ETU	Phase I
5.	Doxorubicin	MM 302	Phase I
6.	Docetaxel	Doxorubicin	Phase I
7.	Annamycin	Liposome-Annamycin	Phase II
8.	Cisplatin	Lipoplatin	Phase II
9.	Doxorubicin	ThermoDox	Phase II

Table 2. Market Product of Liposomes

APPLICATIONS:

- Liposomes as drug or protein delivery vehicles.
- Liposome in antimicrobial, antifungal (lung therapeutics) and antiviral (anti HIV) therapy.
- In tumour therapy.
- In gene therapy.
- In Immunology.
- Liposomes as artificial blood surrogates.
- Liposomes as radiopharmaceutical and radiodiagnostic carriers.
- Liposomes in cosmetics and dermatology. (4)

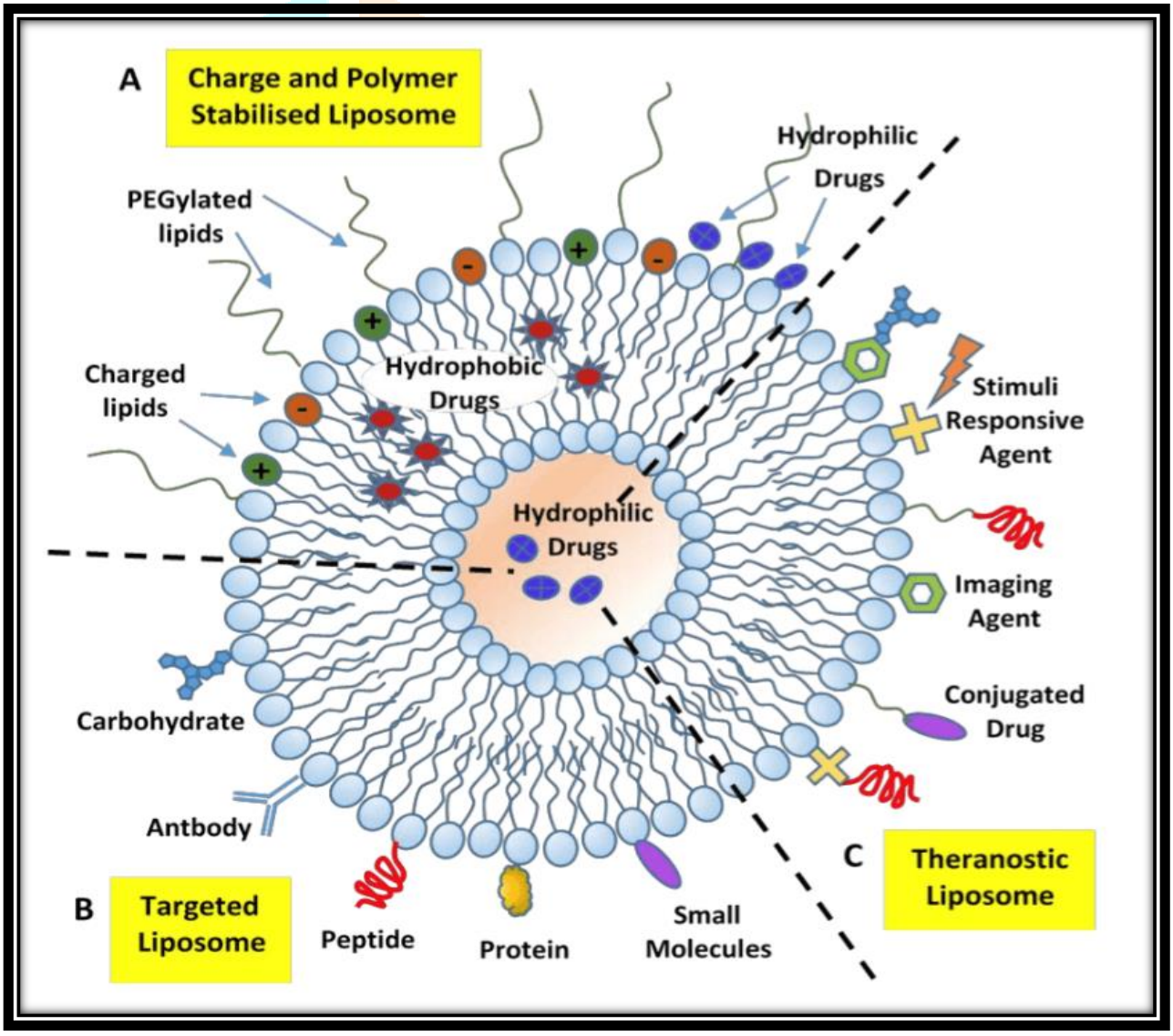

Fig 5. Application

Cancer therapy:

Liposome-based chemotherapeutics used in the treatment of cancer such as breast cancer can improve the pharmacokinetics and pharmacodynamics of associated drugs. Liposome can target a drug to the intended site of action in the body, thus increase its therapeutic efficacy. Anthracyclines are drugs which inhibit the growth of dividing target anti-cancer drugs to cells by intercalating into the DNA and, thus, kill mainly rapidly dividing cells. These cells are not only in tumors but are also in hair, gastrointestinal mucosa, and blood cells; therefore, this class of drug is very toxic. The encapsulation of cytotoxic agents within liposomes allows to accumulation at of anti-cancer drugs at the tumor site. In addition, the presence of the phospholipid bilayer prevents the encapsulated active form of the drug from being broken down in the body before reaching tumor tissue and also serves to minimize exposure of the drug to healthy sensitive tissue. As a result, reduces the toxicity of anti-cancer drugs.(7)

Transdermal drug delivery:

Transdermal DDSs offer a number of potential advantages over conventional methods such as injectable and oral delivery. The main problem to the transdermal delivery system is the limitation of the penetration of macromolecules and hydrophilic drugs through the stratum corneum. The intercellular lipids of the stratum corneum perform a key role in establishing the permeability barrier of the skin. Liposome system is a suitable carrier to improve drug delivery through the skin[66,67] because they are predominantly phospholipids bilayer similar to that existence in biological membranes. Different forms of liposome preparations such as solution, creams, gels, and ointments can deliver compounds across the stratum corneum.

Liposomes have high member fluidity; therefore, they can increase the permeability of skin for various entrapped drugs and deliver drugs to target. From this way and at the same time diminish the side effect of these drugs. In recent years, liposomes have been very much considered as a vesicles for transdermal drug delivery, they are regularly released from the base in topical administration, and also they tend to accumulate in the stratum corneum of the skin and after entering this layer, slowly out of it and enter the circulatory system, therefore, can act as a depot from which the entrapped compound is slowly released over time across skin. As a result, topical drugs are prepared as liposomes compared to traditional local forms, need less drug to create a therapeutic concentration in the local administration site, on the other hand, increase the duration of action and decrease the frequency of administration. As a result, side effects are reduced.

Immunology:

Liposomes rapidly accumulate in macrophages, so this ability can be used in vaccination and activation of macrophages. In immunology, antigens encapsulated in liposomes are developed to create antibodies, to activation passive and active immunization and for many other applications. The first application of liposomal as immunological adjuvant was reported by Allison and Gregoriadis.[73] Today, liposomes are used as

immunological adjuvants in many cases such as hepatitis B-derived polypeptides, subunit antigens from the influenza virus, adenovirus type 5 hexon, allergens, and polysaccharide-protein conjugates. Liposome-based vaccines have been effective in experimental models against the viral, bacterial, parasitic infections, and even tumors. Liposome has been widely studied in adjuvant therapy include hepatitis B-derived polypeptides, subunit antigens from the influenza virus, adenovirus type 5 hexon, allergens, and polysaccharide-protein conjugates.

Antibiotic therapy:

Liposomes increase the effect of antibiotics for two reasons: First, they encapsulate hydrophilic antibiotics such as vancomycin and triclosan and their lipid nature increases the entry of antibiotics into the microorganism cells. As a result, the effective dose of the drug and its toxicity decrease. Second, they protect the entrapped drug against enzymatic degradation. For example, protect the penicillins and cephalosporins from degradation by the beta-lactamase enzyme, which is produced by certain microorganisms

Diagnosis Addition to the therapeutic area, liposomes are also effective in diagnosis cases such as therapeutic imaging modalities, liposomes encapsulate contrast agents and through this are employed in diagnostic X-ray, and nuclear magnetic resonance imaging. [78] Cosmetics In the dermatological and cosmetic field, liposomes are used because of their capability of enclosing many different biological materials and of delivering them to the epidermal cells. The moisture content of the skin has special significance in cosmetic applications, therefore Cosmetic care is concerned to equilibrate the moisture balance of the skin. Liposomes easily are hydrated and can reduce dry skin, which is on factor aging of the skin. [79] In addition, anti-inflammatory agents, immunostimulants, and enhancers of molecular and cellular detoxification within liposomes could prevent age spots, dark circles, wrinkles, and other clinical aspects of skin.

According to the study, on liposomes for targeting drugs into the pilosebaceous units, has observed that liposomes are potent DDSs for treating hair follicle-associated disorders, such as acne.[80] Liposomes can increase tretinoin concentration in the epidermis and dermis and protects it from photodegradation and minimize skin irritation compared to conventional cream or gel, and this way enhance the clinical effect.[81] Briefly, the use of liposomes in nano cosmetology also has many benefits, including improved penetration and diffusion of active ingredients, selective transport of active ingredients, longer release time, greater stability of active ingredients, reduction of unwanted side effects, and high biocompatibility.(11)

CONCLUSION:

The potential use of liposomes in man necessitates the production of sterile, pyrogen free preparations of liposomes which requires specific conditions for their preparation. For use as drug carriers, liposomes should be able to fuse with the arbitrary cells in a spontaneous and controllable manner. One major drawback of liposomal drug delivery system is poor encapsulation of certain drugs in which case the drug is derivised.

Application of liposomes medicine include encapsulation of both Lipid and water soluble drugs. Apart from use as drug carrier perhaps the most promising immunological property of liposomes is their cation as adjuvants. The development of 'pharmaceutical' liposomes is currently a growth area. (12)

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