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A REVIEW ON LIPOSOMAL DRUG DELIVERY SYSTEMS

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Abstract

Liposomes are instinctively set vesicles made of lipid bilayer. Liposomes can be filled with medicines, and used to have covered generally medical, albeit somenon-medical areas like bioreactor, catalysts, cosmetics and ecology. Still, their ascendance in medicine delivery and targeting has enabled them to be used as deliver medicines for cancer and other conditions. Amongst the colorful carrier, many medicine carrier reached the stages of clinical trails where phospholipid vesicles (liposome) show strong eventuality for effective medicine delivery to the point of action. Liposomes can be composed of naturally- deduced phospholipids with mixed lipid chains or other surfactants. Liposome rectifiers tool in fields like tumour targeting, gene and antisense remedy etc. Liposomes are colloidal spheres of cholesterolnon-toxic surfactants, sphingolipids, glycolipids, long chain adipose acids and indeed membrane proteins and medicine motes or it's also called vesicular system. It differs in size, composition and charge and medicine carrier loaded with variety of motes similar as small medicine motes, proteins, nucleotides or plasmids etc.

Keywords

Liposomes; Characterization; Drug delivery; Medicine; Stability

Introduction

In 1965, some researchers printed the primary description of swollen lipoid systems.

among a couple of years, a range of embedded lipoid bilayer structures consisting of single bilayers, at first ‘bangosomes’ and so ‘liposomes’, were delineated . the first pioneers like Gregoriadis and Perrie have established the conception that liposomes will entrap medicine and might be used as drug delivery systems[1].

in vivo activity of liposome-entrapped medicine in animal models

were 1st incontestible by mistreatment the anti-cancer drug C arabinoside to demonstrate vital will increase within the survival times of mice bearing L1210 cancer [2]. From then it became a well-liked ‘model system’ for testing the consequences of a good type of cyst characteristics on therapeutic outcomes. The name cyst springs from 2 Greek words: 'Lipos' which means fat and 'Soma' which means body. A cyst is fashioned at a range of sizes as unilamellar or multi-lamellar construction, and its name relates to its

structural building blocks, phospholipids, and to not its size. Liposomes were 1st delineated by British hematologist Dr Alec D Bangham in 1961 (published 1964), at the Babraham Institute, in Cambridge. They were discovered once Bangham

and R. W. Horne were testing the institute's new microscope by adding negative stain to dry phospholipids.[3,4] planning of liposomes is finished to realize the subsequent optimized properties.

1. Drug loading and management of drug unleash rate
2. Overcoming the speedy clearance of liposomes
3. animate thing delivery of medication
4. Receptor-mediated endocytosis of ligand-targeted liposomes
5. Triggered unleash
6. Delivery of nucleic acids and desoxyribonucleic acid

Mechanism of cyst formation

Liposomes ar fashioned by phospholipids (amphiphilic molecules having a hydrophilic head and hydrophobic tail). The hydrophilic half is especially oxyacid certain to a water soluble molecule whereas the hydrophobic half consists of 2 carboxylic acid chains with 10-24 carbon atoms and 0-6 double bonds in every chain. They type lamellar sheets once distributed in liquid medium by positioning themselves in such the simplest way that the polar head cluster faces outward the liquid region whereas carboxylic acid teams face one another forming a spherical, sac like structures referred to as as liposomes [5]. The polar fraction remains in-tuned with the liquid region together with the shielding of the non-polar half. once phospholipids ar hydrous in water, together with the input of energy like sonication, shaking, heating, homogenisation, etc. it's the hydrophilic/ hydrophobic interactions between lipid-lipid, lipid-water molecules that result in the formation of bilayered vesicles so as to realize a physical science equilibrium within the liquid section. Phospholipids ar the most parts of the cytomembrane thus they possess wonderful biocompatibility with amphiphilic properties. The amphiphilicity give it the property of self assembly, emulsifying and wetting characteristics. once phospholipids introduced into liquid environment, they self assemble and it generates totally {different|completely different} structures with specific properties at different conditions. as an example, phospholipids have a natural tendency to create liposomes, which may use as drug targeting molecules.

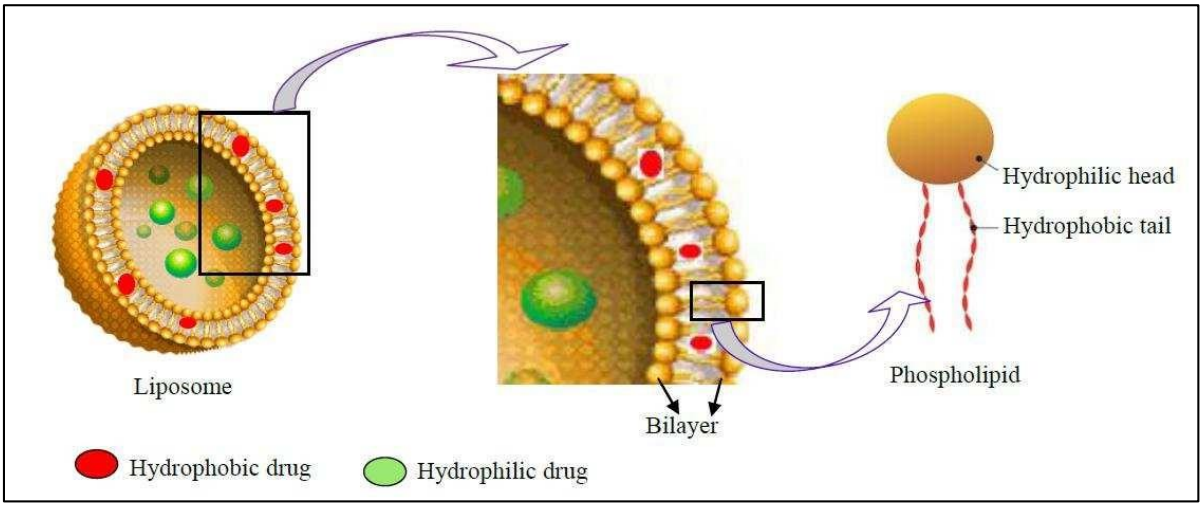
the explanation for bilayer formation includes:

• The unfavorable interactions created between hydrophilic and hydrophobic section which may be reduced by folding into closed concentric vesicles .

• the massive free energy distinction existing between the hydrophilic and hydrophobic setting is reduced by the formation of huge sac formation. The unfavorable interactions created between hydrophilic and hydrophobic section which may be reduced by folding into closed concentric Since spherical structures have minimum physical phenomenon and most stability. thus there's most stability of self assembled structure by forming vesicles.

Liposomes have a characteristic TC (transition temperature), at that they transit from gel section to liquid crystalline section. The encapsulated rugs ar unleash at crystalline section [6]. Liposomes formation is feasible given that the temperature is on top of transition temperature. cyst of pure lipid's transition temperature is forty one.4°C, whereas lipids from natural origin like emulsifier exhibit broad transition temperature [7]The higher limit of temperature for cyst formation is that the Krafft purpose of emulsifier, at 58°C and so temperature vary between forty one.4°C and 58°C is right for cyst formation eg thermosensitive liposomes [8].

Structure of liposome:



Components of Liposome:

There are number of the structural and nonstructural components of liposomes, major structural components of liposomes are:

a. Phospholipids

Phospholipids are the major structural component of biological membranes, where two type of phospholipids exit- PHOSPHODIGLYCERIDES AND SPHINGOLIPIDS. The most common phospholipid is phosphatidylcholine (PC) molecule. Molecule of phosphatidylcholine are not soluble in water and in aqueous media they align themselves closely in plannar bilayer sheets in order to minimize the unfavorable action between the bulk aqueous phase and long hydrocarbon fatty chain.

The Glycerol containing phospholipids are most common used component of liposome formulation and represent greater than 50% of weight of lipid in biological membranes. These are derived from Phosphatidic acid.

Examples of phospholipids are:

1. Phosphatidyl choline (Lecithin) – PC
2. Phosphatidyl ethanolamine (cephalin) – PE
3. Phosphatidyl serine (PS)
4. Phosphatidyl inositol (PI)
5. Phosphatidyl Glycerol (PG)

b. Cholesterol

Cholesterol dose not by itself form bilayer structure, but can be incorporated into phospholipid membranes in very high concentration upto 1:1 or even 2:1 molar ratio of cholesterol to phosphatidylcholine. Cholesterol inserts into the membrane with its hydroxyl group oriented towards the aqueous surface and aliphatic chain aligent parallel to the acyl chains in the center of the bilayer. The high solubility of cholesterol in phospholipid liposome has been attributed to both hydrophobic and specific headgroup interation, but there is no unequivocal evidence for the arrangement of cholesterol in the bilayer.[9-10]

Classification of liposome based on pharmaceutical and therapeutical aspects:

Liposomes can be classified on the basis of size and number of bilayers. They are classified as multilamellar vesicles (MLV), large unilamellar vesicles (LUV) and small unilamellar vesicles (SUV). Based on composition, they are classified as conventional liposomes (CL), pH-sensitive liposomes, cationic liposomes, long circulating liposomes (LCL) and immuno-liposomes. Based on the method of preparation, they are classified [11] as reverse phase evaporation vesicles (REV), French press vesicles (FPV) and ether injection vesicles (EIV) .given in table 1.

Type	Specification
MLV	Multilamellar large vesicles- >0.5µm
OLV	Oligolamellar vesicles- 0.1-1µm
UV	Unilamellar vesicles (all size range)
SUV	Small Unilamellar vesicles- 20-100nm
MUV	Medium sized Unilamellar vesicles
LUV	Large Unilamellar vesicles- >100
GUV	Giant Unilamellar vesicles- >1µm
MV	Multivesicular vesicles- 1µm

Table 1

Stability of Liposomes

The therapeutic effectivity of the drug molecule is ruled by the steadiness of the liposomes involving producing steps, storage, and delivery. A stable indefinite quantity type maintains the physical stability and chemical integrity of the active molecule throughout its organic process procedure and storage. Stability study with planning includes the analysis of its physical, chemical, and microbic parameters along side the peace of mind of the integrity of the merchandise throughout its storage [12].

Physical stability

The vesicles obtained throughout the liposomal formation processes ar of various sizes. throughout its storage, vesicles tend to combination and increase in size to achieve a thermodynamically favorable state. whereas storage, leak of the drug from the vesicles will cause its fusion and breaking. This deteriorates the physical stability of the liposomal drug product. Therefore, the morphology and size distribution of the vesicles ar vital parameters for assessing the physical stability [13].

Chemical stability

Phospholipids ar with chemicals unsaturated fatty acids, susceptible to oxidisation and reaction, which can alter the steadiness of the drug product. pH, ionic strength, solvent system, and buffered species conjointly play a significant role in maintaining a liposomal formulation. oxidisation deterioration involves the formation of cyclic peroxides and hydroxy-peroxidases thanks to the results of atom generation within the oxidisation method. Liposomes will be prevented from aerobic degradation by protective them from light-weight, by adding anti-oxidants like like butylated hydroxyl radical dissolvent (BHT), manufacturing the merchandise in associate degree inert surroundings (presence of chemical element or Argon), or by adding EDTA to get rid of trace significant metals [5].

Plasma Stability
Although liposomes agree biomembranes, they still ar foreign objects for the host. Therefore, liposomes ar recognized by the mononucleate somatic cell system (MPS) when interaction with plasma proteins. As a result, liposomes ar cleared from the blood. These stability issues solve by mistreatment artificial phospholipids, gangliosides, chemical change, coating liposomes with polysaccharide derivatives, lyophilization, microencapsulation, and particle coated with amphipathic synthetic resin glycol.

TECHNIQUES OF CYST PREPARATION
in several preparation procedures, a general pattern will be discerned.[14]
GENERAL ways OF PREPARATION
All the ways of formulating the liposomes involve four basic stages:
A. Drying down lipids from associate degree organic solvent.
B. Dispersing the supermolecule in binary compound media.
C. Purifying the resultant cyst.
D. Analyzing the ultimate product.
1] association stage
A] Mechanical Methods: MLVs were by tradition made by hydrating skinny lipids films placed from associate degree organic answer on a glass wall by shaking at temperatures higher than the action temperature of the lipid with the topmost Tc. The wide size distributions of the shaped cyst dispersions were typically tapering down by tiny pressure extrusion instead ultrasonication.[15]
B]Methods supported detergent removal: Phospholipids, lipotropic compounds, and amphipathic proteins will be solubilized by detergents forming mixed micelles. Upon elimination of the detergent, sac formation will occur. this method is well established for the preparation of reconstituted virus envelopes [16] or reconstituted tumour membrane material.[17] Schreier and coworkers delineate a ballroom dance strategy for the insertion of proteins into the outer layer of liposomes. 1st liposomes were shaped by the detergent qualitative analysis methodology and later, macromolecules were inserted by partial re-solubilization of the membrane by the detergent (deoxycholate) within the presence of protein. [18]
C] methodology supported size transformation and fusion: Sonication of phospholipids below their action temperature [Tc] ends up in vesicles with defects within the bilayers. Heating the dispersion to Tc eliminates these structural defects and causes fusion leading to massive unilamellar liposomes with a large size distribution.[19] the most disadvantage of this method is that the restricted range of bilayer composition that reacts and also the poor duplicability of the particle size distribution of the cyst dispersion that's shaped.
2] filler stage
There ar 2 approaches, one while not a special filler step [A] and one with a special filler step [B]
[A]In the cyst formation method, circumstances ar designated and controlled in such the simplest way that particle size distributions with a suitable breadth ar made. High shear blend produces a size distribution that depends on operational pressure. [20,21,22]
[B] Removal of nonencapsulated material
Many lipotropic medication show a scoop affinity to the bilayer and ar fully cyst connected. Though, for different compounds, the encapsulation effectivity is fewer than 100%. The non-encapsulated fraction of the spirited compound will produce unacceptable facet effects or physical instability.[16] For removal of nonencapsulated material, the following ways ar used:
a) qualitative analysis and ultra-centrifugation.
b) Gel permeation natural process.
c) action reactions.
Therapeutic Applications of Liposomes
Liposomes give superior therapeutic effectivity and safety compared to existing formulations. a number of the foremost therapeutic applications of liposomes in drug delivery include:

Intracellular drug delivery
Increased delivery of potential medication to the cytoplasm (where drug receptors ar present) will be accomplished by mistreatment LDDS. N-(phosphonacetyl)-L-aspartate (PALA) is generally poorly obsessed into cells. Such medication once encapsulated at intervals liposomes, showed larger activity against female internal reproductive organ tumour cell lines compared to the free drug [25].

Sustained unleash drug delivery
To achieve the optimum therapeutic effectivity, which needs a protracted plasma concentration at therapeutic levels, liposomes give sustained unleash of
target medication [26]. medication like pyrimidine Arabinoside will be encapsulated in liposomes for sustained unleash and optimized drug unleash rate in vivo.

Intraperitoneal administration

Site-avoidance delivery The toxicity of anti-cancer medication to traditional tissues is attributed to their slender therapeutic index (TI). below such circumstances, the TI will be improved by minimizing the delivery of medicine to traditional cells by encapsulating them in liposomes. For eg antibiotic drug features a severe facet result of internal organ toxicity, however once developed as liposomes, the toxicity was reduced with none modification within the therapeutic activity [23].

Site-specific targeting
Delivery of a bigger fraction of the drug to the specified (diseased) website, reducing the drug's exposure to traditional tissues will be achieved by site-specific targeting. On general administration, long-circulating immunoliposomes will acknowledge and bind to focus on cells with larger specificity [24]. E.g. in patients with continual osteogenic sarcoma, there was associate degree increased tumoricidal activity of monocytes, once muramyl amide derivatives were developed as liposomes and administered systemically.

Tumors that develop within the intra-peritoneal (ip) cavity is treated by administering the drug to science cavity. however the speedy clearance of the medicine from the science cavity leads to decreased quantity of drug at the unhealthy website. However, liposomal encapsulated medicine have lower clearance rate, compared to free drug and might give a most fraction of drug in a very prolonged manner to the target website [27].

Immunological adjuvants in vaccines
Stealth liposomes contain few biological species as a matter to modify binding with specific expression on the drug delivery website (targeted site) additionally to PED coating. These targeting ligands can be, vitamins, specific Associate in Nursingtigens or being antibodies (making an immuno-liposome), however it should be obtainable. Naturally harmful medicine is less harmful systemically if delivered to the unhealthy tissues or website. Ligands used for targeting to lungs for treatment of T.B. embrace maleylated bovine albumin (MBSA) and O-steroyl amylopectin. Transfersomes (a form of liposomes) area unit extremely deformable vesicles, used for stratum material delivery (non-invasive method) [28].

List of chemically approved liposomal drugs

Name	Trade name	Company	Indication
Liposomal amphotericin B	Abelcet	Enzon	Fungal infections

Liposomal amphotericin B	Ambisome	Gilead Sciences	Fungal and protozoal infections
Liposomal cytarabine	Depocyt	Pacira (formerly Skye Pharma)	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	Skye Pharma, Endo	Postsurgical analgesia
Liposomal verteporfin	Visudyne	QLT, Novartis	Age-related macular degeneration, pathologic myopia, ocular histoplasmosis
Liposome-PEG doxorubicin	Doxil/Caelyx	Ortho Biotech, ScheringPlough	HIV-related Kaposi's sarcoma, metastatic breast cancer, metastatic ovarian cancer
Micellular estradiol	Estrasorb	Novavax	Menopausal therapy

CHARACTERIZATION OF LIPOSOMES

Both physical and chemical characteristics of liposomes influence their behavior in vivo and in vitro. [29] cyst characterization ought to be performed in real time once preparation.

A. Liposomes for cistron Delivery

It is important to dissect the cell uptake method into individual steps. In fact, numerous studies have indicated that productive cistron transfer in vitro involves:

1] the packaging of deoxyribonucleic acid,
2] the adhesion of prepackaged deoxyribonucleic acid to the cell surface,
3] acquisition of deoxyribonucleic acid,
4] escape of deoxyribonucleic acid from endosomes if endocytosis is concerned,
5] deoxyribonucleic acid expression in cell nuclei.

To do all of the on top of steps, liposomes are discovered as a delivery system for deoxyribonucleic acid as early as in 1979. [30] The encapsulation of inclusion body deoxyribonucleic acid into liposomes [31] and therefore the introduction of enterovirus RNA and SV40 deoxyribonucleic acid into cells via liposomes [32,33]were rumored between 1979 and 1980.

Ph sensitive cyst Strategy

1] Liposomes of varied compositions will extensively bind to cell surfaces. For cistron transfer, it had been well-known that dioleylphosphatidylethanolamine [DOPE] is out and away the foremost effective supermolecule for in vitro cistron transfection for pH-sensitive liposomes or as supermolecule helper in cationic liposomes. [34,35,36,37]

2] it's been expected that the aim of phosphatidylethanolamine [PE] is that of a membrane fusion supporter, since in reality this supermolecule suffers changes upon activity. [38] steroid alcohol is usually essential to attain ample stability of those liposomes. The arrangement of liposomes might play associate chief role in

their communications with cells. the dimensions of liposomes in addition because the variety of cells ar elementary for associate economical capture by cells. Generally, liposomes ar obsessed by numerous endocytosis processes. skilled phagocytes like macrophages and neutrophils will take up liposomes of varied size and charge through active bodily process. The sac pathway for cellular uptake. once binding to the cell surface, liposomes ar internalized into endosomes wherever they encounter a a lot of acidic pH scale than within the external medium. Early endosomes typically have an enclosed pH scale of vi.50.[39,40]

3] The last demand for inclusion body liposomes once cell penetration is to avoid accumulation specially cell compartments like lysosomes. so as to stop this degradation, pH-sensitive liposomes are planned.[34,35] pH scale-sensitive liposomes were designed supported the thought of viruses that fuse with the endosomal membrane by suggests that of supermolecule at pH pH scale, delivering their genetic material to the cytoplasm before reaching the lysosomes.[41,42] typically, the supermolecule accustomed style pH scale sensitive liposomes is alphabetic character. alphabetic character represents a young girl of lipids that, once distributed in pure kind, assemble into non-bilayer structures in n inverted polygonal shape part.[38]

4] A key question remains regarding the mechanism of pH-sensitive liposomes: do they react as originally intended? Ropert et al. [43,44] encapsulated antisense oligonucleotides into pH-sensitive liposomes, a brief length of deoxyribonucleic acid directed against the env cistron of the murine Friend animal virus, to inhibit virus proliferation. They counseled that the bigger action of oligo-nucleotides encapsulated into pH-sensitive cysts wasn't because of a weakening of the DOPE liposome bilayer however to associate improved association between pH-sensitive liposomes and cells. They delineate that the effectualness of the infective agent inhibition gained with oligo-nucleotides encapsulated into PH-sensitive liposomes was one doubly that of oligo-nucleotides encapsulated into non-PH-sensitive liposomes. And a two-fold growth in cell connotation was conjointly detected once once liposomes were compared to PH-insensitive liposomes. In fact, pH scale-sensitive liposomes ar obsessed a lot of with efficiency by cells than pH insensitive liposomes, a truth in all probability resulting in an improved activity. [45]

CATIONIC supermolecule STRATEGY

The encapsulation of deoxyribonucleic acid into standard liposomes can be a technical issue because of the inclusion body size, representing a poor transfection system. On this basis, another procedure supported cationic lipids and alphabetic character was developed within the late Nineteen Eighties. [36] the thought was to neutralize the charge of plasmids with charged lipids to capture plasmids a lot of with efficiency and to deliver deoxyribonucleic acid into the cells. Generally, this is often an easy procedure requiring admixture the cationic lipids with the deoxyribonucleic acid and adding them to the cells. This ends up in the formation of aggregates composed of deoxyribonucleic acid and cationic lipids. The cationic supermolecule DOTMA was initial synthesized and delineate by Felgner et al. This lipid, conjointly alone or together with additional neutral lipids, impetuously formulae multilamellar vesicles (MLV) which could be sonicated to create tiny unilamellar vesicles (SUV). deoxyribonucleic acid intermingles impetuously with DOTMA to create deoxyribonucleic acid complexes by suggests that of 100% of the deoxyribonucleic acid changing into connected. it's likely that advanced formation merely results from ionic interactions between the charged headgroup of DOTMA and therefore the charged phosphate teams of DNAs. DOTMA is commercialised [Lipofectin., Gibco-BRL, Gaithersburg, MD] as a 1 to 1 mixture with DOPE and has been wide accustomed transfect a large type of cells.[46,47,48,49]

LIPOSOME FOR TARGETED DELIVERY

Usage of cyst encapsulated enzymes for delivery into cells was initial declared in 1971. At an equivalent time, a definite receptor on hepatocytes was confirmed to mediate clearance of ß-galactose completed glycoproteins from movement. A mannoside-specific receptor was recognized on the cell surface of the RES of rats [including the liver sinusoid and macrophages]. By graft completely different glycosides on the surface of liposomes, it's doable to direct the latter to completely different cell sorts of rat liver.[50]

CONCLUSION

Twenty 5 year of analysis into the employment of cyst in drug delivery. Liposomes ar one among the distinctive drug delivery system, which may be of potential use in dominant and targeting drug delivery. Liposomes ar administrated orally, parenterally and locally in addition as utilized in cosmetic and hair technologies, sustained unharness formulations, diagnostic purpose and pretty much as good carriers in cistron delivery numerous medicine with liposomal delivery systems are approved. today liposomes or used as versatile carriers for targeted delivery of drug.

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