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A REVIEW ON LIPOSOMAL DRUG DELIVERY SYSTEM

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ABSTRACT

Liposomes is lipoids bilayer, which have been first prepared by Bangham and others in 1961. They having extraordinarily drug entrapment efficiency. Due to their size, hydrophobic and lipophilic character they're most extensively used cars for drug shipping. The main goal of this drug transport gadget is to target the drug immediately to the website online of movement so that you can lengthen and decorate the drug effect. Liposomes are biologically compatible and are able to entrap hydrophilic as well as lipophilic drug inside its compartment. The are available in different sized varies from 0.05-5.0µ in diameter. Numerous convectional techniques used for liposomal preparation and size reduction are mechanical dispersion strategies, solvent dispersion strategies and detergent elimination approach. Due to distinction in method of preparation and composition of lipids, liposomes may be characterised in step with length, price, lamellarity and so forth. This text provide a top level view of liposomes, benefits, disadvantages, mechanism of movement, classification, structural composition, training as well as evaluation parameters, programs and future elements.

KEYWORDS: Liposomes, Bilayer vesicles, Drug entrapment, Hydrophobic, Hydrophilic Etc.

INTRODUCTION

In the early 1960's Bangham and colleagues observed the liposomes which have become most broadly used drug drug delivery device.[1] Liposomes are used for to treat the tumor focused on, antisense and gene therapy, genetic vaccination, immune modulation, lung therapeutics, fungal infections and pores and skin care and topical beauty merchandise.[1] Liposomes are phospholipid bilayer vesicles wherein an aqueous volume is completely enclosed through a lipid bilayer membrane made up of herbal or artificial phospholipids. 'Lipos' approach fats and 'Soma' approach body. [Patel Chirag et al., (2020)]

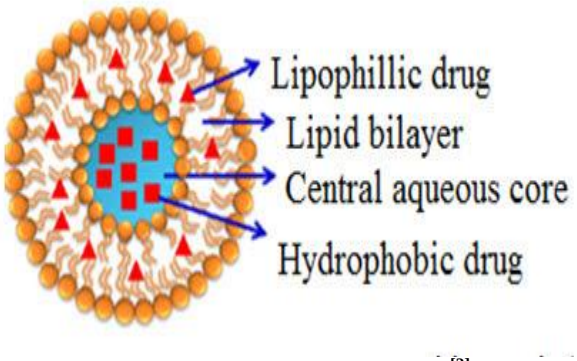


Fig. 1: Structure of liposome.[2]

Advantages of liposomes[1,2,3]

- Biocompatible, non- toxic, biodegradable.
- Selective passive focused on to tumour tissues.
- Expanded healing index and efficiency.
- Decreased toxicity.
- Managed and sustained launch.
- Minimize side effect.
- Encapsulation enhances balance.
- Appropriate for hydrophobic, amphipathic and hydrophilic pilDisadvantages/Hazards of liposomes[1,3]

Disadvantages/Hazards of liposomes[1,3]

Following IV management, liposomes are unexpectedly excreted from the body by means of reticula endothelial system cells and Kupfer cells.

- Reduces the stability and solubility of the drug.
- Shorter organic half-life.
- Growth manufacturing price.
- Phospholipids may additionally go through oxidation or hydrolysis.

The lipid membrane of liposomes is made up of an amphiphile forming a bilayer, ldl cholesterol and a rate producing molecule.[1]

Liposomes are fashioned after hydration of phospholipids (amphiphilic molecules with a hydrophilic end and a hydrophobic head). The hydrophobic quit incorporates fatty acid chains with 10-24 carbon atoms and zero-6 double bonds in each chain. The polar foot, i.e. the hydrophilic head, consists of phosphoric acid certain to a water-soluble molecule.[4]

Whilst they're dispersed in aqueous medium they arrange themselves to form lamellar sheets in which the polar head institution faces outwards to the aqueous location and fatty acid companies forms a spherical vesicle like structure dealing with every different, called as liposomes. The polar region remains in touch with aqueous region and shields the non-polar component.[5]

The hydrophilic/hydrophobic interaction between lipid-lipid or lipid-water molecules results in the formation of bilayer vesicles which arrives at a thermodynamic equilibrium inside the aqueous section. This happens best when phospholipids are hydrated in water with input of electricity like homogenization, shaking, sonication, and many others.[4,5]

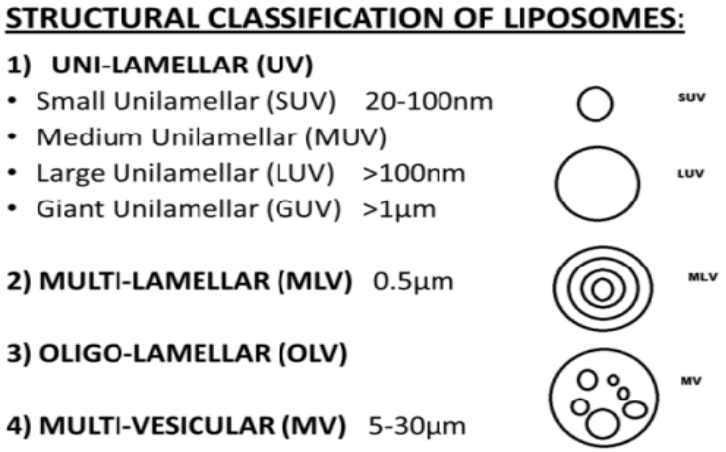
Vital parameters affecting bilayer formation are[1]

- Hydrophobic interaction together with the amphiphilic nature of the main phospholipid molecules is the motive for bilayer structure of liposomes.
- Due to the excessive differences in unfastened strength between the hydrophobic and aqueous surroundings, the bilayer structure is raised to reap the bottom unfastened strength degree.
- Notable molecular self-assemblages can gain maximum stability via forming into vesicles via precise molecular geometry.

Types/Category of liposomes[1,37-46]

Liposomes are produced via diverse techniques and their nomenclature relies upon on their technique of instruction, special capabilities or their structural parameters.[1]

Table 1: Classification of liposomes.



Structural composition

1) Phospholipids:

Phosphatidylcholine (laptop) is one of the most usually used phospholipids in liposome instruction. It may be obtained from each natural and synthetic resources. It includes a hydrophilic group with a quaternary ammonium moiety choline, that's linked via phosphoric ester to a glycerol. The hydrogen chain of lipid molecules ensures the stableness of liposome membrane.[6] Glycerol containing phospholipids are most commonly used element in liposome formulation.[7]

Examples of phospholipids are[12]

- Phosphatidyl choline (Lecithin) – computer
- Phosphatidyl ethanolamine (Cephalin) – PE
- Phosphatidyl serine (playstation)
- Phosphatidyl inositol (PI)
- Phosphatidyl glycerol (PG)

2) Sphingolipids

Sphingolipids are a class of lipids which can be essential component of both plant and animal cells.[7] Sphingolipids are shaped from palmitoyl CoA and serine. Cell makes use of sphingosine to form ceramide. Ceramide are structural gadgets of all Sphingolipids and

are shaped from long chain of fatty acids and sphingosine. Most commonly used sphingolipids are sphingomyelin, glycosphingolipids. Sphingomyelins are handiest form of phospholipids which do no longer have a glycerol backbone.[8]

3) Sterols

Sterols are cholesterols or derivatives of cholesterols which is probably used to decrease bilayer fluidity, lower permeability of water and increase the steadiness of the bilayer within the biological environment.[9] Liposomes without cholesterol swiftly react with plasma protein consisting of albumin, transferring, and macroglobulin which results in extract bulk phospholipids from liposomes, accordingly depleting the outer monolayer of the vesicle inflicting bodily instability.[10] Inner the eye ratio of 1:1 or 1:2, cholesterol is covered in phospholipids. LDL, cholesterol enters into the membrane via its hydroxy institution going through the aqueous environment and phospholipid bilayer acetyl chain placed parallel to the acyl chain within the middle of the bilayer. With the useful resource of its incorporation lipid bilayer may be changed consequently increasing its stability. Every hydrophilic and unique head organization interplay ensures high solubility of LDL cholesterol in phospholipids liposomes.[13,14]

4) Synthetic phospholipids[1,11]

Artificial phospholipids are a kind of phospholipids wherein precise molecular species of polar head corporations or fatty acids are introduced through chemical synthesis method.

Examples for saturated phospholipids are:

- Distearoyl phosphatidylcholine (DSPC)
- Dipalmitoyl phosphatidyl glycerol (DPPG)
- Examples for unsaturated phospholipids are:
- Dioleoyl phosphatidyl glycerol (DPOG)
- Synthetic phospholipids have been essentially designed to optimize the drug targeting houses of liposomes.

5) Polymeric materials

within the Hydrocarbon chain, artificial phospholipid with diactylenic organization even as exposed to UV results in formation of polymeric liposomes having better permeability barrier to encapsulate aqueous tablets. Example: For exceptional polymerizable lipids - lipids containing conjugated diene, methacrylate and so forth. Additionally several polymerizable surfactants also are synthesized.[10]

6) Polymeric bearing lipids

Stability of repulsive interaction with macromolecules is ruled via repulsive forces. As a consequence via manner of coating liposome floor with charged polymer the repulsion may be brought on. Polymeric bearing lipids are organized with the aid of polymerization of lipid membrane which extensively stabilizes the membrane architecture with the aid of way of directly covalent coupling of adjoining lipid molecule.[10]

Polyethylene oxide polyvinyl alcohol and polyoxazoline are example of non-ionic and water well matched polymer having higher solubility for the duration of absorption because of hydrophilic section and hydrophobic part of such copolymer, leads to liposome leakage, so fine consequences may be finished by covalently attaching polymer to phospholipids. Examples: Diacyle Phosphatidyl Ethnolamine with PEG polymer linked via a carbon at or succinate bond.[11]

7) Cationic lipids

Cationic lipid is a undoubtedly charged amphiphile which incorporates three structural domains: i) a undoubtedly hydrophilic head organization; ii) a hydrophobic portion composed of a steroid or of alkyl chains; iii) a linker connecting the cationic head organization with the hydrophobic anchor.[15]

Examples: DODAB/C: Dioctadecyl dimethyl ammonium bromide or chloride.

DOTAP: Dioleoyl propyl trimethyl ammonium chloride – an analogue of DOTAP and various others consists of various analogues of DOTMA and cationic derivatives of LDL cholesterol.[10]

8) Other substances[16]

- In case, if the drug is liable to oxidation, various antioxidants are used along with tocopherol, butylated hydroxy toluene.
- Form of stabilizers are used to form stable liposome
- Preservatives are also used to growth the shelf life of liposomal formulation.

Preparation of liposomes[47-59]

Liposomes are especially organized two strategies thru passive loading techniques and with the aid of energetic loading strategies.

Passive loading techniques encompass 3 exclusive methods:

I. Mechanical dispersion technique
II. Solvent dispersion technique
III. Detergent removal technique

Passive loading techniques

I. Mechanical dispersion method[1]

1. Skinny movie hydration the usage of hand shaking (MLVs) and non-shaking techniques (ULVs)

those techniques includes casting of lipids as stacks of films from their natural answer both the use of flash rotary evaporator beneath decreased stress or via hand shaking determined with the useful resource of dispersion of casted movies into aqueous solution. Upon hydration the lipids swell and flake off from the spherical bottom flask's wall and vesiculate to form MLVs. In hand shaking approach, mechanical electricity is imparted by the usage of guide agitation and in non-

shaking technique power is imparted by way of the usage of exposing the movie to stream of water saturated nitrogen for 15 min. the share encapsulation overall performance as excessive as 30% may be finished.

2. Micro-fluidization

Micro-fluidization method is likewise known as micro-emulsification that is used for big scale production of liposomes.[17] It's a long way especially a today's method which incorporates the pressure of the two motion of liposomes suspension colliding with each exclusive underneath excessive pressure to reduce the vesicle length. Uniformly hydrated phospholipid suspension (unisized liposomes) is transferred to the reservoir. Through the interaction chamber the liposome suspension is pumped beneath pressure. Further, to deliver smaller and additional uniformly sized liposome, the suspension is break up into streams and then recombined at high tempo inside the interplay chamber.[18]

The suggest vesicle length of the liposome reduced extensively to zero.1 and 0.2 µm in diameter after three passes via micro fluidizer.

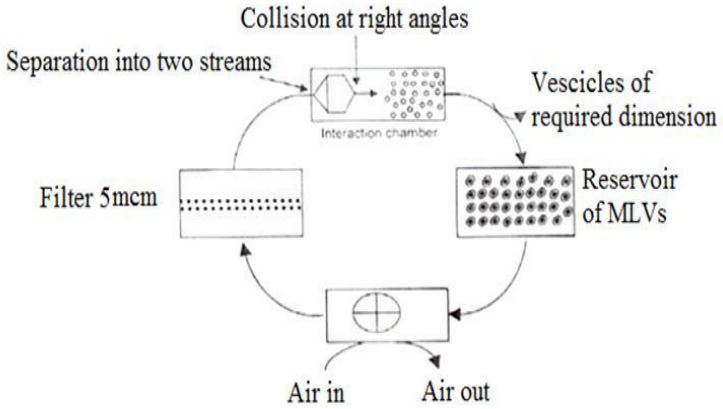


Fig. 2: Liposomes prepared by Micro-fluidization method.[1]

3. Sonication

Sonication is the maximum widely used approach for guidance of SUV's. At better strength levels, the common length vesicles are similarly decreased. Here, the MLV's are exposed to ultrasonic irradiation.[1]

Types of sonicators are used i.e. a Probe sonicator and a bath sonicator. Probe sonicator is used for dispersions having strength in small volumes (instance- excessive lipoidal attention or a viscous aqueous section). The strength supplied via the probe tip into the lipid dispersion could be very excessive. Tub sonicators are used for huge volumes of diluted lipids.[1,19]

The prepared SUV's are purified by way of ultracentrifugation. Negative aspects of sonication approach are: low encapsulation performance, metal pollutants from probe tip, phospholipid degradation and presence of some MLV's at the side of SUV's.[3]

4. French pressure cell

In this method "unit or oligo lamellar liposomes" of intermediate length of 30-80 nm in diameter are yield relying on the carried out pressure.[1] Underneath high pressure, passage via a small orifice, dispersion of MLV'S may be transformed to SUV's. In French stress mobile MLV's dispersion are extruded at about 20,000psi at 45°C. The approach is speedy and reproducible. The liposomes long-established by way of this method are large than sonicated SUV's. Few drawbacks of this technique are excessive temperature required is hard to gain and running volumes are smaller (almost 50 ml because the max).[20, 21]

5. Dried Reconstituted Vesicles (DRV'S)

This technique entails freeze drying of a dispersion of an empty SUV followed by means of its rehydration with aqueous fluid containing the fabric to be entrapped.[1,22] Liposomes fashioned from DRV approach are zero.1µm or much less in diameter i.e. uni- or oligo-lamellar liposomes. Excessive entrapment of water soluble components and use of mild conditions for arrangements and loading of bioactive are the primary advantages of this approach.[22]

6. Freeze Thaw Sonication (FTS) technique[1,3,19,23,24]

FTS method is an addition to the classical DRV technique. SUV's are rapidly frozen and thawed by means of sanding at room temperature for 15 min accompanied by subjection to a sonication for a short period of time. The unilamellar vesicles are fashioned because of the fusion of SUV all through the methods of freezing and thawing. The entrapment efficacy varies from 20% to 30%.

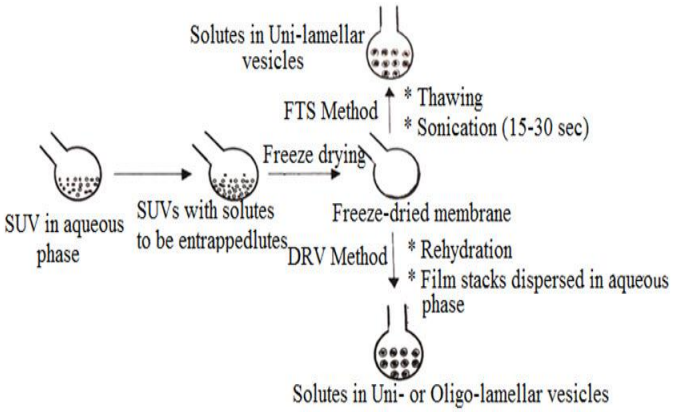


Fig. 4: Liposomes organized by Dried Reconstituted Vesicle (DRV's) and Freeze Thaw Sonication (FTS) technique.[1]

Membrane extrusion technique

Membrane extrusion is a way wherein the liposome suspension is handed thru membrane clear out of defined pore size so one can reduce the dimensions of liposomes. This method is used to system LUV'S and MLV'S. The gadget is equipped with a pump that pushes fluid or the instruction via the membrane to accomplish the extrusion system. There are two kinds of membrane filter for this technique, the tortuous path kind and nucleation track kind. Diverse styles of extruders are Lipex extruder, Extruder®, Avestin liposofast TM 50 and many others. Various parameters of extrusion method are implemented strain, number of cycle, pore size affect the mean diameter and length distribution of the organized liposomes. The process is simple, reproducible inhibit phospholipid degradation which increases the encapsulation efficiency of the liposome guidance. The encapsulated quantity is 1-2 liters/mol of lipid.[1,25,61]

II. Solvent dispersion technique

1. Ether injection approach

A lipid solution is dissolved in ether ethanol aggregate or diethyl ether is injected slowly thru a slim needle into an aqueous answer of fabric to be encapsulated at the temperature of vaporizing the natural solvent or beneath decreased strain which sooner or later leads to the formation of liposomes. The publicity of the compound to be encapsulated at higher temperature, ends in their degradation which may be avoided by using the use of fluorinated hydrocarbon (Ferons) instead of ether. The performance of liposomes shaped is exceedingly low, although the extent encapsulated in step with mole of lipid stays high eight-17/mol.[19,60]

2. Ethanol injection

A rapid injection of an ethanol solution of lipid, through a great needle into an excess of saline or other aqueous medium. To reap whole blending, infusion is performed at excessive rate in order that the ethanol is diluted hastily in water and dispersion of phospholipids molecule happens during the medium. This technique yields excessive percentage of SUV'S (~25), although if the aggregate isn't at some stage in enough lipid aggregates and larger vesicles may also shape.[1] The primary benefit of the method is use of non-harmful solvent together with ethanol. the main disadvantage of the technique are heterogeneous population is formed (30-110nm), very dilute liposomes are fashioned as ethanol paperwork azeotrope with water consequently it is difficult to get rid of all ethanol and the presence of even low amount of ethanol can lead to inactivation of diverse biologically lively molecule.[26]

3. Reverse phase evaporation approach

Similarly to the above injection approach, numerous phospholipids (natural/mixed with cholesterol) can be used in this technique.[27] In a round backside flask, the lipid combination is brought and with the aid of the rotary evaporator the solvent is removed under pressure. The device is purged with nitrogen. The lipid is re-dissolved within the natural segment, in which reversed phase vesicles might be formed.[28] The 2 phase system is sonicated until the combination becomes clear one segment dispersion, also known as inverted miscells. Via the assist of rotatory evaporator the natural solvent is eliminated slowly until, inverted miscells are transformed into viscous country and gel bureaucracy. The gel nation collapses at a essential thing on this approach, and some of the inverted miscells are disturbed. The following liposomes are known as opposite face evaporation vesicles (REV). Excessive encapsulation fee as a great deal as 50% is the primary advantage of this method.[1,5]

III. Detergent depletion (removal)

In this, the phospholipids are offered in intimate touch with the aqueous segment thru detergents, which partner with phospholipids molecules. The structures fashioned due this affiliation are known as 'micelles'. The shape and length of the micelles relies upon at the chemical nature of the detergent, awareness and other lipids worried. Vital Micelle attention (CMC) is the awareness of detergent in water at which micelles begin to form. Underneath CMC detergent molecules stays in free

solution. Whilst awareness of brought detergent is expanded extra quantity of detergent is integrated into the bilayer until the conversion from lamellar to round micelles takes place. On further growth in concentration of detergent, the micelles are reduced in size.[1,62]

Energetic (remote) loading

On this approach, internalization of preformed liposomes is normally pushed through manner of a trans-membrane pH gradient. The pH surrounding the liposome allows a number of the drug to stay in unionized form, therefore, permitting it emigrate at some stage in the lipid bilayer layer. As soon as, in the liposomes, the drug turns into ionized and gets entrapped right here due to the difference in pH.[1]

Advantages of active loading method over passive encapsulation strategies are-

- A high encapsulation efficiency and capability.
- A reduced leakage of encapsulated compounds.
- Restricted chemical degradation in the course of garage.
- Avoidance of organic active compounds throughout guidance steps within the dispersion as a consequence reducing safety dangers.

Evaluations

After system of liposomes they're evaluated to be expecting their in vitro and in vivo performances.[1,3,10]

The characterization of liposomes is specially categorised in 3 classes together with bodily, chemical and biological parameters. Bodily parameters consists of size, shape, surface functions, lamerallity, section behaviour and drug launch profiles. Chemical parameters consist of studies which prove the purity and potency of various liposomal elements. Organic parameter allows in organising the safety and suitability of arrangements for therapeutic use.

1) Vesicle shape and Lamellarity

Vesicle form may be decided the use of various electron microscopic techniques, and also can be used to determine the average particle length. Lamellarity of the vesicle i.e., the extensive form of bilayers gift within the liposomes is evaluated the usage of Freeze-fracture electron microscopy and 31P nuclear magnetic resonance assessment.

2) Vesicle Size and Length distribution

Various strategies are describes within the literature for dedication of size and size distribution. Those methods encompass light microscopy, fluorescent microscopy. Electron microscopy, laser light Scattering, Photon Correlation Spectroscopy, Gel Permeation and Gel Exclusion and Zetasizer. Electron microscopy is the most precise approach however hence could be very time consuming.

a) Microscopic strategies

i. **Optical microscopy:** Vesicle length of massive vesicles (>1µm) can be decided using bright discipline, contrast and fluorescent microscope.

ii. **Transmission Electron Microscopy (TEM):** the use of bad stain TEM helps estimation of the liposome length range on the decrease give up of the frequency distribution. Bad stains used in TEM evaluation are Ammonium Molybdate, Uranyl Acetate and Phosphotungstic acid.

iii. **Cryo-Transmission Electron Microscopy method (Cryo-TEM):** it has been used to assess size of the vesicles and surface morphology and extensively utilized to symbolize liposomal formulations in which the drug is loaded by using faraway loading to ensure their stability. The approach entails freeze fracturing of the samples accompanied with the aid of their visualization the use of TEM.

iv. **Freeze Fracture Electron Microscopy:** its miles particularly used to decide the floor capabilities and lamerallity. It is able to also be used to calculate true vesicle diameter.

b) Diffraction and Scattering techniques

i. **Laser light scattering:** Laser based totally, quasi-elastic mild scattering strategies are useful to research the homogenous colloidal particulate populations. This approach is based on the time based coherence of mild scattered with the aid of a vesicle. It can be implemented to systems with suggest diameter much less than 1µm.

c) Hydrodynamic strategies

These strategies encompass Gel permeation, field glide Fractionation and Ultracentrifuge strategies.

3) Surface charge

Zeta potential and free flow electrophoresis are used to look at fee on the vesicle floor. Vesicle floor price is calculated from the mobility of the liposomal dispersion in a suitable buffer.

4) Encapsulation efficiency

It determines the amount and charge of entrapment of water soluble agents within the aqueous compartment of the liposomes.

Applications[1,3,10]

1. Liposomes as protein drug shipping vehicle:

- Altered bio distribution and pharmacokinetics
- In situ sustained and managed drug launch.
- Enzyme alternative remedy
- Lysosomal garage diseases
- Increased solubilization of medication
- Altered bio distribution and pharmacokinetics

2. Liposomes in gene diseases

- Gene and antisense remedy
- DNA vaccination

3. Liposomes as providers for vaccines.
4. Liposomes as vendors for tablets in oral remedy.
5. Liposomes for topical applications.
6. Liposomes for pulmonary shipping.

7. Liposomes against Leishmaniasis.
8. Liposomes for ophthalmic shipping of medicine.
9. Liposomes in immunology:
- Immune adjuvant
- Immune modulator
10. Liposomes as artificial blood surrogates.
11. Liposomes in bioreactors and enzyme immobilization generation.
12. Liposomes in antifungal, antimicrobial, and antiviral treatments

Future aspects[9,29,30]

Thinking about liposomal drug transport machine inside the destiny, novel drugs may be transformed into convectional liposomes with enhanced flow. Shipping of ribozymes and oligonucleotides is likewise confident in destiny. Encapsulated allergens and blood primarily based artificial liposomes are the destiny applicant for improvement and are utilized in allergy remedy as desensitizer. Immunotherapy, diagnostic assay and targeted transport of drugs are three major areas for development in future. By using the usage of liposomal package with synthetic composition of lipid bilayer, for the dimension reproducible consequences may be acquired. Meals, cosmetics, vitamins and coating industries etc are unique areas of liposomal development in future. Spatial and temporal launch of liposome encapsulated capsules at site of movement is one of the routes that name for destiny improvement in remedies.

CONCLUSION

Liposomes have been diagnosed as surprisingly beneficial provider structures and gear for targeted drug delivery. Liposomes are attaining medical suggestions due to their superior drug shipping to the diseased locations. Liposomes are of unique interest as intracellular shipping systems for anti-experience molecules, ribosome, proteins/peptides, and DNA. The bendy behavior of liposomes and their decreased toxicities are utilized for drug delivery via any direction of management and for any drug or cloth irrespective of their physiochemical residences. But, based at the pharmaceutical applications and available product, we will say that liposomal drug transport has a first-rate promise in the destiny and is positive to go through in addition tendencies.

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