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A review on perspective of liposome in drug delivery system

Radheshyam Samanta, Manoj Kumar Dandpat and Abhijit Satpathy

Abstract
Novel drug delivery system is defined as the advance drug delivery system which improves drug potentiality followed by drug release for sustained augmentation of desirable pharmacological activity. The main aim and objective of novel drug delivery system (NDDS) is to provide bioavailability of a particular drug in specific site in our body. Now a day's novel drug delivery system is more beneficial than conventional delivery of drug because of their more therapeutic activity, active targeting and long circulation in our body. Most of this liposome is effective nano vesicle carrier drug delivery system developed for delivery of different drugs, protein, peptides, DNA and immunological product. The liposome based drug delivery system is mainly used to treat inflammation, cancer, parasitic diseases. The industrial application include the use of liposome as drug delivery carriers in pharmacotherapy, adjuvant and vaccination, signal accelerators in clinical diagnostic and in bio analytical chemistry, Solubilizers for various ingredients and penetration enhancer in cosmetics.

Keywords: Novel drug delivery system, bioavailability, liposome

Introduction
The fundamental concept of liposomal drug delivery system was come in the pharmaceutical science which was proposed by Alec Bangham, in 1961 [1]. The name of liposome is derived from two Greek words "Lipid" meaning fat and "Soma" meaning body (Lipid body) [2]. Liposomes are a novel drug delivery system they are microscopic vesicles in which an aqueous volume is entirely enclosed by a membrane composed of lipid bilayers. A liposome is a small spherical which contain the same material as like as a cell membrane. It composed of drugs and other material that are used as a carrier mediate for drug delivery system in different disorder in our body like cancer, inflammation etc. Liposomal membranes are generally made by phospholipids that contain two groups one is hydrophilic head group and other is hydrophobic tail group. The head is attracted to water, and the tail, which is prepared by long hydrocarbon chain, is repelled by water [3-4]. Liposome is used to modifying the characteristic of old and new drugs for improving their absorption reduce metabolism, long circulation and reduce toxicity. Lipids forming liposomes contain several polymers, its may be natural or synthetic polymer, for their biocompatibility and biodegradability, they can be used very influencely in medical science. The special characteristic of liposome to encapsulated both hydrophilic and hydrophobic materials by nature. This unique feature, coupled with biocompatibility and biodegradability make liposomes very attractive as drug delivery system. Hydrophobic drugs incorporated tail of the phospholipids bilayer of the liposome and hydrophilic drugs are encapsulated within the aqueous compartment or at the bilayer head. The formulation of liposome improves the therapeutic activeness of drugs in humans binges compared to conventional drug delivery system due to the modification of bio distribution. Liposome containing drug show good pharmacological activity in our body because they target specifically and biological inert or stable and produced low toxicity in our body. Liposomal drug delivery system gives a broad idea for drug delivery, cosmetics technology and molecular structure of the membrane. Liposomes are colloidal system, having a size range of 0.01-5.0 µm in diameter generally formed bilayer vesicle for evaporating the solvent and lipid form a bilayer incorporation with water (Fig-1) [5-19].

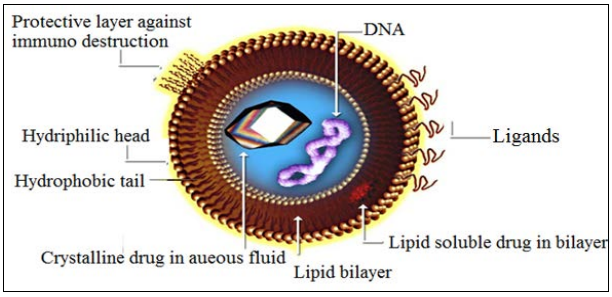

Fig 1: Schematic diagram liposomes

Features of liposomes [20]

1. Control release of drug in suitable targeted area in our body.
2. Long circulation in our body by presence of polymer on their surface that reduces the quick clearance in our body.
3. Delivery of drug inside the cell.
4. Specific ligand targeted receptor mediated drug delivery system.
5. Liposome do not interact with encapsulated drug or reduce their activity.
6. They are available in various size and shape.
7. Ability to protect the labile components.
8. Having a good power for administered for water soluble and lipid soluble drug.
9. Including drug they also deliver immunological product, protein, peptide, DNA, nucleic acid etc.

Advantage of liposomes [2, 5]

1. It improves therapeutic effectiveness of drug.
2. It proposes specific and targeted delivery of the drug.
3. Both hydrophilic and hydrophobic or lipophilic drug can be delivering in our body.
4. It does not produce toxicity of some sensitive drug in our body tissue.
5. It improvises a wide range of size for delivery of drug.
6. They have good comfort ability like biocompatible, biodegradable, non-immunogenic and non-toxic.
7. Liposome is administered in our body in different route.

Disadvantage of liposomes [2, 5]

1. Biological half-life of liposome is very short.
2. They are expensive preparation so highly economical.
3. Bioavailability problem sometime due to instability.
4. It shows poor solubility.
5. There will be chance of leakage due to encapsulation of drug molecule.
6. It produces hypersensitivity reaction in our body.
7. There may be chance of oxidation and hydrolysis due to the presence of lipid component.

Composition of liposomes

The fundamentals of liposomes are composited with the help of lipid that is phospholipids and other component is cholesterol that is not a lipid but a stabilizer to maintain the structural composition of liposomes

Phospholipids

Our body containing biological cell membrane is similar composition of phospholipids, this phospholipid structure having two layer one is hydrophobic tail and another is hydrophilic head, this hydrophobic part contain hydrocarbon polymeric chain and head contain hydrophilic phosphate group [21]. The most important phospholipid is used in the preparation of liposome that is phosphotidylcholine (Choline base) because of their most availability and stability depending upon the cell membrane and environmental condition of drugs [22]. Another lipid that is sphingolipid (Sphingoid base) are also used in the preparation of liposomes, sphingomyelins is the most important example of phospholipid that help for formulation of liposomes, another type of phospholipid that may also used in the formulation of liposomes that is phosphatidylethanolamine, phosphatidulserines, besides this glycolipids and sterols are also used to prepare liposomes (Fig-2) [23].

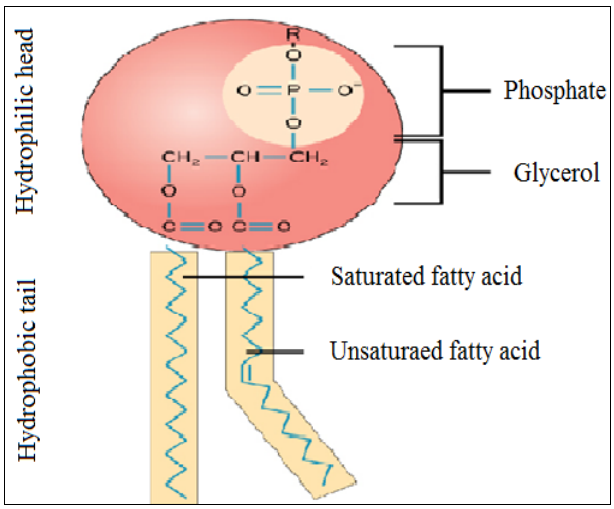

Fig 2: Structural diagram of phospholipid

Cholesterol

Cholesterol is also used as a component that structurally combined with phospholipids to maintain their stability, flexibility, smooth and also improves the liposomes circulation to whole circulating system in our body [24, 25]. Cholesterol do not produced any bilayer of phospholipids they help to combination in the formation of bilayer with 1:1 or 1:2 (Phospholipids: cholesterol) resolution incorporation to maintain their stability, and they incorporated in between hydroxyl group in the aqueous surface and lining of acyl hydrocarbon chain on the centre of the molecule (Fig-3).

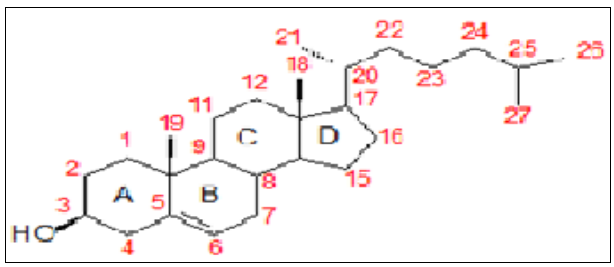

Fig 3: Structural diagram of cholesterol

Classification of liposomes

Liposomes are classified according to their different characteristic or properties, according to this liposome are mainly classified into three types.

1. Liposomes are classified based on structural size and lipid bilayer or lipid lamellar (Fig-4) [26-28]

a) ULV-This liposomes is prepared by single bilayer of lipid with varying depending upon their size they can classified as SUV (20-40 nm), MUV (40-80 NM), LUV (100-1000 NM), GUV (Greater than 1000 nm).
b) OLV- These liposomes are prepared by 2 to 5 bilayer of lipid encapsulated in a large internal volume. They have a diameter in between 100 to1000 nm.
c) MLV- These liposome are prepared by series of concentric lipid bilayer (5-20 layer) encapsulated in a small internal volume. They have a diameter in-between 1000 nm or more than.
d) MVV- These liposomes are prepared by multicompartment structure of lipid bilayer having a diameter more than 1000 nm.

2. Liposomes are classified based on their preparation method

a) REV- Reverse phase evaporation method
b) MLV-REV- Multilamellar vesicles prepared by reverse phase evaporation method
c) SPLV- Stable plurilamellar vesicles
d) FATMLV- Frozen and thawed multilamellar vesicles
e) VET- Vesicles prepared by extrusion technique
f) DRV- Dehydration rehydration method

3. Liposomes are classified based on their composition and application method

a) Conventional liposomes- they composed by neutral or negatively charge phospholipids and cholesterols.
b) Fusogenic liposomes- they composed of reconstitutd sendai virus envelops.
c) PH sensitive liposomes- phospholipids such as PER or DOPE.
d) Cationic liposomes- cationic lipids with dope.
e) Long circulating liposomes- neutral high temperature, cholesterol and 5-10% PEG, DSP.
f) Immune liposomes- CL or LCL with attached molecular antibody or recognition sequence.

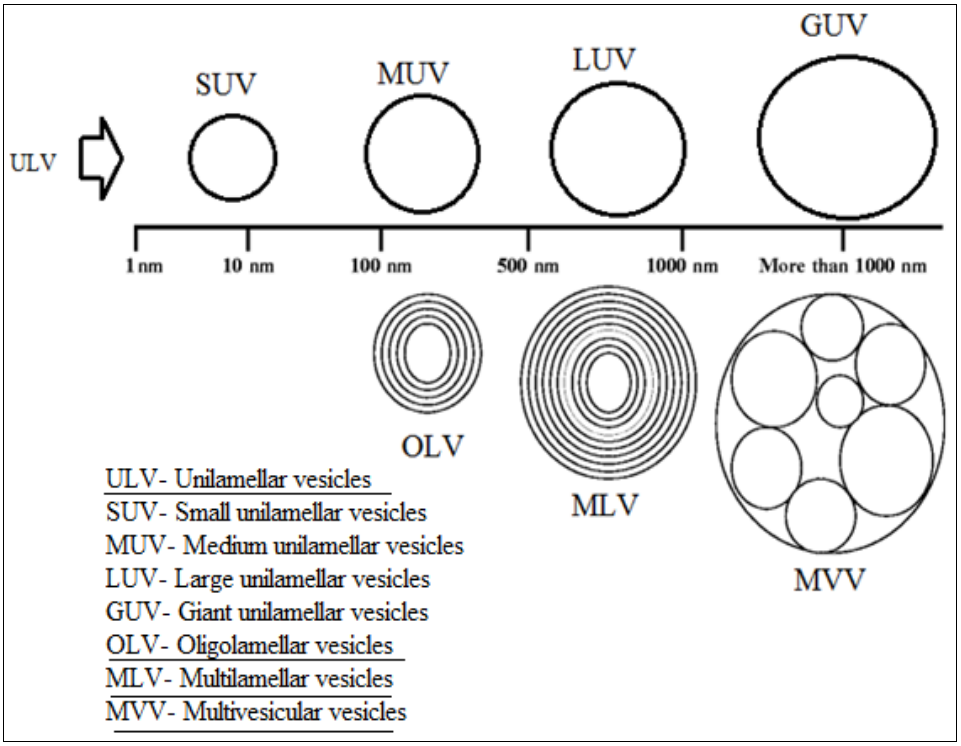

Fig 4: Schematic diagram of liposomes according to different sizes and number of lipid lamellar

Mechanism and delivery of drug through liposome [20]

Liposomes contain generally two region one is hydrophilic region where the aqueous drur are encapsulated inside the lipid bilayer and another is hydrophobic region that is the membrane of the liposome where the oily or lipidic drug are encapsulated and to deliver both hydrophilic and lipophilic drug. The target of drug delivery depending upon the characteristic and composition of drug molecule and lipid, that the encapsulated drug containing liposomes are penetrate same characteristic cell membrane bilayer and to produced activity.

There are several steps involving of liposomal delivery of drug:

1. First liposomes are adsorbing to the cell membrane and retain on the cell membrane.
2. This adsorption is conducted through the surface of the cell membrane followed by engulfing method and penetrating.
3. Blending of lipid bilayers of liposomes with the lipophilic cell membrane by tangential diffusion and assortment of lipids result in direct delivery of liposomal contents in the cytoplasm.
4. Similar characteristic of cell membrane and lipid bilayer of phospholipid, protein transfer conducted to the cell membrane and lipid transfer to delivery of characteristic drug.

Preparation method of liposomes

There are several methods available for the preparation of liposomes, Most of this method are described about the passive encapsulation of drugs. So the preparation method of liposomes are given to a chart (Fig-5) and also described about the some of this method.

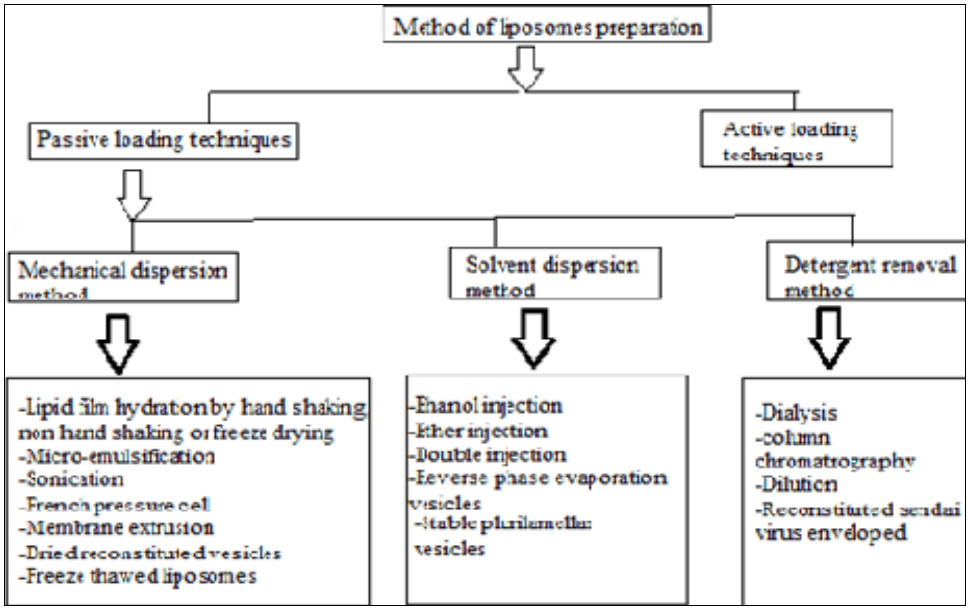

Fig 5: Chart diagram for preparation methods of liposomes

Lipid film hydration using hand shaking method

At first phospholipids and cholesterol are incorporated in the organic solvent. After that this organic solvent are removed by evaporating the organic solvent using rotary evaporator under reducing pressure. Then this dried phospholipid film are hydrated with already drug incorporating aqueous solvent and agitate the mixture by maintaining above the lipid transition temperature and produces multilamellar vesicles liposomes with different shape and sizes. This method are generally used for the preparation of liposomes [29].

Sonication method

This method are used to prepare different small unilamellar vesicles with high energy level lipid suspension, in generally a audio wave (Sonicate) are produces in the suitable container contain liposomal mixture. There are two type of sonication method are available for their preparation i.e.1) probe sonication method- in this case liposomes are produces in small quentities because of the high energy level in lipid suspension containing liposomes and most disadvantages is that produces high amount of heat 2) bath sonication- this is most suitsble for more quintities of liposomes without producing heat at different shape and size including unilamellar liposomes [30].

French Pressure Cell Method

French pressure cell method are used to converted multilamellar vesicles to unilamellar vesicles. This method containing multilamellar vesicles are extruded 20000 psi at 4° Celsius through the small orifice and converted small ULV, this is very simple and rapid method but they are larger as compares to sonication method and the major disadvantage maintaining of temperature and weighted volume [31].

Membrane Extrusion method

In this method insoluble lipid are obtained by dissolving in organic solvent then organic solvent are evaporated with the help of evaporator then they are aqueous solubilised with buffer solution incorporating with drug of this dried lipid layer then sonicated to ultra-waved passing (extrusion) through the polycarbonate membrane filter and obtain uniform size liposomes [21].

Freeze and Thawed method

This is also very effective method for preparation of liposomes to encapsulated protein and peptides type of molecules. In this method first the solute containing compositor are extruded with the help of whirled to form film suspended composition and this composition are freezing and then warming or heating continuously within periods of six cycling of freeze and thawed mean heating this MLV are converted suitably ULV of their obtaining uniform size extrusion are required [32].

Ethanol Injection Method

In this method ethanol solution containing lipid are injected to the buffer solution or drug containing aqueous buffer solution then multilamellar vesicle are formed but in that case liposome are very diluted in form and the lamellar is not for a suitable in size. The most important demerit of this method is that difficulty to the removal of ethanol and they produce difficult in stability of these liposomes [3].

Ether Injection Method

In this method lipid containing ether solution are injected to a drugs containing aqueous solution at high temperature or under reducing pressure then this ether are removed to creating vacuum and prepare liposomes. The main demerit of this type of liposomes is same as to ununiform formation like ethanol injection system and also requiring high temperature for their production [33].

Reverse Phase Evaporation Method

This is very useful method for preparation of efficient liposomes. In this case reverse phase is evaporated and formed liposomes, firstly two phase like one is aqueous and another is organic like ether containing lipid are taken with encapsulating drug with proper sonication then form water in oil emulsion after that to form a viscous gel while organic solvent are removed revesly under reducing pressure. This method are used to encapsulated both large and small drugs molecule and more efficient when taking low ionic strength

containing 0.01M Nacl as an aqueous phase [34].

Detergent Removal method

This method is very useful to preparing same size liposomes.in this method are generally used to removing the detergent by the help of dialysis method, detergent are generally used to remove the surface or interfacial tension in between different component of liposomal mixer and lipid are solubilised at a concentration of detergent that is called critical micelles concentration (CMC) and this micelles are composited with phospholipids and detergent are removed with suitable method to produces large unilamellar vesicles. Another technique has been used for the removal of detergents:

a) By using Gel Chromatography involving a column of Sephadex G- 2 [35].
b) By adsorption or binding of Triton X-100 (a detergent) to Bio-Beads SM-2 [36].
c) By binding of octyl glucoside (a detergent) to Amberlite XAD-2 beads [37].
d) The main merit of this method is reproducibility and demerit is small trace of detergent are present in the liposomes [35].

Parameter characterization of liposomes for their stability

For maintaining their stability like different physical, chemical and biological properties, characterization should conducted of their different component concentration or parameter value of liposomes by using several analytical method or technique.

Table 1: Chemical Charecterization [38-39]

Parameters	analytical method
Phospholipids concentration	HPLC/Barrlet assay
Cholesterol concentration	HPLC/Cholesterol oxide assay
Phospholipids per oxidation	U.V observation
Ph	pH meter
Osmolarity	Osmometer
Phospholipids hydrolysis	HPLC and TLC
Drug concentration	Assay method
Cholesterol auto-oxidation	HPLC and TLC

Table 2: Physical Charecterization [40-45]

Parameters	Analytical method
Vesicle shape and surface morphology	TEM and SEM
Vesicle size and size distribution	Dynamic light scattering TEM
Surface charge	Free flow electrophoresis
Electrical surface potential and surface Ph	Zeta potential measurement and pH sensitive problems
Lamellarity	P^{31}NMR
Phase behaviour	DSC, freeze fracture electron microscopy
Percent capture	Mini column centrifugation
Drug release	Diffusion cell/dialysis

Table 3: Biological Charecterization [46]

Parameters	Analytical method
Sterility	Aerobic/anaerobic culture
Pyrogenicity	Rabbit fever response
Animal toxicity	Monitoring survival rats

Application: Liposomes are very effective for drug delivery system with their advanced technology. In current condition this liposomes are more applicable for their drug delivery system that describe under below.

1. Targeting of drug deliver to the specific site

Administration of large quantity of drug to the specific site of our body and also reduce the activity of drug to normal tissue effect and this polymeric immunoliposomes are circulate in our systemic circulation and bind to specific site of our targeting cell or tissue to produce their activity [47].

2. Control (Sustained) drug delivery

Liposomes are effectively achieved the sustain release of drug because they circulate long time in our body so release of drug solely for a long time in our body that can maintain the high blood plasma level concentration to achieved the effective therapeutic efficacy in our body [48]. The cytosine Arabinoside, cortisone, vesopressin drug can be encapsulated in liposomes for sustained release and optimized drug release rate.

3. Site-avoidance therapeutically active delivery

The toxicity effect of some anti-cancer drug to minimize their toxicity to other cell or tissue and also achieve maximum therapeutic index and easily pass through the blood brain barrier to specific targeting of brain cancer are encapsulated in liposomes. For eg doxorubicin and amphotericin B has a severe side effect of cardiac toxicity, but when formulated as liposomes, the toxicity was reduced without any change in the therapeutic activity [49].

4. Penetrating of tissue and intracellular drug delivery

Liposome drug delivery system can easily penetrate any tissue and deliver the drug for producing their activity as example anaesthetic and insulin. This liposome containing active drug can also penetrate intracelluarly and attached to the cytosol receptor site that can produced the active action as example N-(phosphonacetyl)-L-aspartate is normally poorly taken up into cells but this drugs when encapsulated within liposomes, produced much more activity against ovarian tumor cell in comparison to free drug [50].

5. Intraperitoneal prolong drug administration

Megaloblastic tumor are easily grown to the intra peritoneal system so in that case when normal drug delivery system are used to deliver the drug then they produces quick clearance to prevent this activity liposomal drug delivery system are preferred example acyclovir [51].

6. Local or topical Drug Delivery

Lipid bilayer and structural cell membrane, several dermatological problem like skin inflammation, skin allergy activity the liposomal drug delivery system are preferred for their moisturizing and restoring capability [52].

7. Cosmetics delivery

The liposomal property is also help for delivery of cosmetics materials to the skin appearance beautification. The liposome composited with lipid that are compatible with skin layer so easily transportation should conducted and also restoration of phospholipids and linolenic acid [53].

8. Immunogenic activity

This is most important application of liposomes because

long circulation and attaching of antibody or ligand on the surface of liposomes for their targeted drug delivery and these type of liposome are called as immunoliposomes and produce activity or release drug to combine with specific site of this ligand containing receptor [54-55].

9. Genetic delivery of liposomes

Gene and genetic material are easily supply through liposomes like DNA, RNA, Nucleotides etc. into cellular nucleus. In generally bioengineering liposomes like PH sensitive liposomes, cationic liposomes, niosomes are usefull for gene delivery of drug [56].

10. Liposomal delivery of nutritional agent to treat disease

Most important nutritional agent is protein and peptides that can easily transport to the complicated area in our body through the liposomes and cure the complication whether the normal protein and peptides are decomposed and degraded to produce instability in our body [57].

11. Treatment of infection

Many pathogenic microorganisms like bacteria, virus, fungi etc. are produce various infections in our body part like liver, spleen, and kidney. This infected disease candidiasis, aspergelosis, histoplasmosis, erythrococosis are very dangerous to their treatment, in that Case liposomes are very effective for encapsulating anti-infective or anti-microbial agent to specific targeting and easily cure this complication [58].

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