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Review of Preliposomes as novel drug delivery system

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Abstract

Liposomes colloidal drug delivery system is broadly applicable for the novel drug delivery systems. Provesicular drug delivery system like preliposomes having distinct advantages over conventional drug delivery system. Conventional liposomes having the problem associated with instability to overcome that problem preliposomes were discovered by Payne *et al.* in 1986. Preliposomes are dry powder, having free-flowing granular products composed of phospholipid and drug which, upon hydration with water, disperse and form a multi lamellar liposomal suspension. Preliposomes composed of water soluble porous powder as carrier which having ability to rapid hydration of preliposomes and formed vesicles. New concept of demonstrating preliposomes as novel carrier to enhance the oral bioavailability and permeation across the membrane. On basis of investigation it is clear that preliposomes are the alternate drug carrier for the various route of administration. These reviews give the brief knowledge about the preparation, evaluation and application of provesicular drug delivery system in pharmaceutical field.

Keywords: Preliposomes, novel drug delivery, vesicles, lipids, carrier

1. Introduction

Liposomes are discovered by Bangham *et al.*, they are continue and most broadly applicable in highly research area for novel drug delivery system [1]. Structurally liposomes contains phospholipids which are biocompatible, biodegradable, nontoxic and not having any allergic or pyrogenic reactions. Phospholipids having capacity to encapsulate smallest lithium ion and large genetic materials of several thousand Daltons [2, 3]. Liposomes have been extensively use for the site specific drug delivery, increased solubility, controlled release, sustained release, prevent the drug degradation for the drug which are affected by the gastric pH [4]. Liposomes having some instability problems physical instability and chemical stability like phospholipid hydrolysis, aggregation and fusion which limit shelf life of liposomes. One of more importance consideration associated with phospholipids are the backbone of the bilayer. Two types namely peroxidation of unsaturated acyl chains which accelerates liposome breakdown and alters drug-release characteristics and hydrolysis of the ester bonds linking the fatty acids to the glycerol backbone [4, 5]. Liposomes required specific storage condition due to its instability. There is Various approaches have been used to overcome instability problems associated with liposomes by provesicular drug delivery system which include, control of particle size and lamellarity, altering the lipid composition, electrosteric stabilization and lyophilization. One approach which helped to overcome the stability issue associated with liposome and led to the development of a provesicular novel drug delivery system is the Preliposome. Discovered by Payne *et al.* in 1986, Preliposomes are dry, phospholipid(s) which, upon addition of water, disperse to form a multi-lamellar liposomal suspension. This is one of the most cost-effective and widely used methods for producing commercial liposome products. Preliposomes having the intrinsic property of hydration in which lipids membrane formed the vesicles when contact with aqueous media. Preliposomes available in the dry powder form, easy to distribute, transfer, measure and store making it a versatile system. Liposomes can be formed *in situ* under the influence of physiological fluids or can be formed *in vitro* prior to administration using a suitable hydrating fluid. Liposomes formed on reconstitution are similar to conventional liposomes and more uniform in size and having high stability. Preliposomes are given in the form of dry powder for pulmonary drug delivery, tablet, and capsule for oral, buccal, and rectal route. Preliposomes enhanced the oral bioavailability of drug which are poorly water soluble and having the extensive first pass metabolism. This review gives a brief overview of advantages disadvantages, preparation, evaluation and application of Preliposome as carrier for targeted drug delivery system. Free-flowing granular products composed of drug(s) and Advantages:

- Preliposomes having combined the solubilizing and protection properties of liposomes with the stability and ease of administration of a solid tablet formulation, as a new delivery system for challenging drugs.
- Improves the dissolution rate and bioavailability of drug
- Increase half-life and Sustain release of the drug can be achieve
- Carry Both hydrophilic and lipophilic drug
- Biodegradable, biocompatible, flexible
- Targeted drug delivery or site specific drug delivery
- Stabilization of entrapped drug from hostile environment
- Alter pharmacokinetics and pharmacodynamics of drug
- Dry free-flowing granular product could be hydrated immediately before use and can avoid many of the problems associated with aqueous vesicular dispersions.
- The new emerging concept has demonstrated the potential of preliposomes/proniosomes in improving the oral bioavailability and permeation of drugs across the stratum corneum.
- Based on the investigations it is clear that provesicular systems appear to be an alternate drug carrier for various routes of drug administration.

1.3 Types of Preliposomal system

1. Dry granular type of preliposomes
2. Mixed micellar preliposomes
3. Liquid crystalline preliposomes

Dry granular type of preliposomes

It is a dry free flowing granular product which can be hydrated immediately before use and is composed of water soluble porous powder as a carrier upon which one can load phospholipid and drugs can be dissolved in an organic solvent. The lipid and drug are coated on the carrier material by using modified rotary evaporator. The lipids are swelled upon addition of water to the dried lipid coated powder preliposomes where the support rapidly dissolves to give suspension of MLVs. The storage of this product as a dry powder, which is hydrated immediately before use. The dry powder of preliposomes can be administered oral, intravenous or other routes. Desirable characteristics of the carrier material given below.

- 1) Good water solubility-for ease of preliposome preparation
- 2) Poor solubility of chloroform and methanol for ease of processing
- 3) Suitability of intravenous use

2) Mixed micellar Preliposomes

It involves bile salts which are 24-carbon 5b cholanoates conjugated to glycine or taurine and hence possess detergent like amphiphilic properties. In the bile, they are responsible for solubilisation of free cholesterol and phospholipids in mixed micelles. This mixed micelle contains bile salts, cholesterol and phospholipids which upon dilution undergo micelle to vesicles transition to form liposomes beyond the mixed micellar boundaries. This system is advantageous in incorporating lipophilic drug without precipitation on aqueous dilution. This system can be administered intravenously or by other routes other than transdermal as the system is in liquid form.

3) Liquid crystalline Preliposomes

It is another type of preliposomes which involves organization of lipid/ethanol/water mixture into the lamellar structure and

can be utilized for transdermal delivery of drugs. When the surfactant crystals are in contact with water, there are three ways in which the lipophilic chain of the surfactant can be transformed into disordered liquid state called lyotropic liquid crystalline state: 1) Increase the temperature at the craft point (tc) 2) Addition of solvent 3) Use of both solvent and temperature. By the use of three ways, the lipophilic chains are transformed in to a disordered liquid state and water penetrates between the polar hydrophilic layers to form a lyotropic liquid crystalline structure (neat phase). When mixture is cooled below the Kraft point, the hydrocarbon chains crystallize and arrange themselves in a lattice with water still present between the polar groups. This is referred to as the gel phase. This gel phase represents the liquid crystalline Preliposome. The liquid crystalline structure provides higher solubility and greater diffusion of the active substance such as hydrocortisone and the system is thermodynamically stable. The diffusion coefficient of the drug in liquid crystalline phase was four times higher value than the corresponding value for the skin. The proliposomal gel provides stability to the formulation and is non-irritating to the skin. It provides higher solubility to the added compound.

Factors Effecting Preliposome Formulation

1) Total lipid concentration: The percentage encapsulation efficiency of the drug was increased as the lipid concentration was increased. The increase in percentage encapsulation efficiency of drug as a function of total lipid concentration was linear.

2) Drug concentration: Increasing drug concentration in the Preliposomes prepared showed an increase in both percentage encapsulation efficiency and the amount of drug encapsulated per mol.

3) Charge of the lipids: Incorporation of either dicetyl phosphate (DCP) which induces negative charge or stearylamine (SA) which induces positive charge decreased the percentage encapsulation efficiency of drug in vesicles.

4) Effect of Phosphatidylcholine (PC) -to-Cholesterol Ratio: The percentage drug entrapment efficiencies of preliposomes can be prepared at various amount ratios of PC to Cholesterol, which reveals that incorporation of more Cholesterol would yield higher EE (%) at a constant molar ratio range. The content of Cholesterol is one of the important parameters in the design of proliposomal preparations, as well as liposomes. Cholesterol does not itself form the bilayer structure but it can be incorporated into the phospholipid bilayers. Since it is amphipathic, Cholesterol could be inserted into the membrane with its hydroxyl group oriented toward the aqueous surface and the aliphatic chain aligned parallel to the acyl chains in the center of the bilayer. But, when the Cholesterol content is over a range, it might lower the partitioning of drug molecules to the bilayer membrane, the degree of encapsulation would decrease. As can be seen, the entrapment efficiencies of all proliposomal formulations were found to be significantly enhanced with the increasing Cholesterol content. The enhancing effect of Cholesterol on the entrapment efficiency may be attributed to the rigidifying effect in the fluid crystal state, facilitating the complete formation of the vesicles with the bilayer-bound drug during the process of preliposome formulation.

5) Effect of total lipid-to-sorbitol ratio: The concentration of sorbitol has no measurable effect on EE% of CT, based on comparison of total lipid: sorbitol ratios from 1: 10 to 1: 20. However, from the point of preparation, it is difficult to prepare the preliposomes when the total lipid-to-sorbitol ratio is higher than 1: 10. Because only a very small volume of the solution of membrane-forming components can be introduced and sprayed onto the limited amount of sorbitol each time, the spraying-evaporating process becomes much time consuming. Because a higher sorbitol concentration did not improve the formation, 1: 10 sorbitol was used for the formulation of preliposomes.

Method of Preparation

Preliposomes can be prepared by following methods:

- 1) Film deposition on carrier method
- 2) Fluidised bed method
- 3) Super critical anti-solvent method
- 4) Slow spray coating method
- 5) Coacervation phase separation method
- 6) Spray drying method

1) Film deposition on carrier method

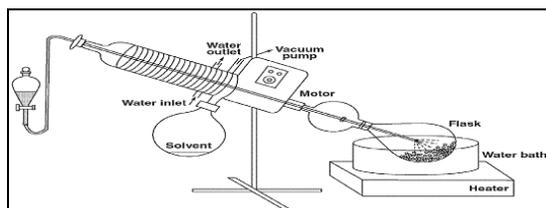


Fig 1: Film Deposition on carrier method

Formation of film of drugs and lipids onto a water soluble carrier material. Solution of drug and phospholipid in an organic solvent is added dropwise by feed tube onto a carrier material in to a rotary evaporator flask under vacuum to form a free preliposomal powder. The carriers should have a high surface area, high porosity, and highly water soluble due to that rapid hydration of preliposomes. Example of carriers Mannitol maltodextrin, sorbitol, etc. This method is tedious and difficult to control, since discontinuous step of solvent addition and evaporation is time consuming. To solve this problem, Xu¹² *et al.* modified in this method carrier, drug, and phospholipid was dispersed in organic solution in the flask of rotary evaporator, and subjected to vacuum evaporation. This process is continuous and time saving compared to the original method.

2) Fluidised bed method

This method is used full for large scale production of Preliposomes based on the principle of particle coating technology. The carriers used in this method are crystalline powder and pareil beads. In this method formation of a thin uniform coating of lipid around the core and small sized liposomes formed on hydration. Solution of drug, lipid and organic solution is sprayed onto the carrier and to remove trace amount of residual solvent the product can be dried under vacuum overnight

Advantages

Film coating technology well developed and processable. Different types of cores and coating materials are available to prepare preliposomes.

This method is cost effective for the preparation of liposomes for novel drug delivery.

3) Super critical anti-solvent method

Supercritical anti solvent method utilizes Supercritical Carbon dioxide (SCCO₂) in the preparation of Preliposomes. SCCO₂ is a fluid state of carbon dioxide where it is held at or above its critical temperature and pressure. Antisolvent technique is widely used in food industry and also to prepare Preliposomes because of its lower residual solvents, simple steps and low operating temperatures. The apparatus used in the preparation of Preliposomes include three parts: Sample delivery unit, Precipitation unit, Separation unit

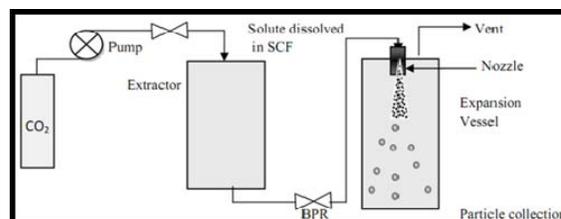


Fig 2: Schematic Presentation of SCF Technology

The sample delivery unit consists of two pumps: one for CO₂ and for solution.

The precipitation unit consists of a heated vessel, separation unit having a separator and wet gas meter.

4) Slow spray-coating method

Spraying of organic solution containing mixture of lipid and drug onto the carrier and solvent is evaporated. This step is repeated to achieve desired lipid loading, because the carrier is soluble in the organic solvent. After formation of preliposome powder when hydration is done the carrier dissolved, and formation of liposomes.

Liposomes have uniform size and shape, similar to liposome prepared by conventional methods.

Advantage

Formation of liposomes of hydrophobic drug without problem of instability.

Disadvantage

In this method sorbitol is used as carrier for preliposomes because sorbitol is soluble in the solvent and it also interferes with entrapment efficiency of drugs.

5) Coacervation phase separation method

In this method weighed amount of phosphatidylcholine and cholesterol at various ratios in the clean and dry, wide mouth glass vial. Drug was added to the lipid mixture with the ethanol to formed homogenous dispersion, the vials is sealed to prevent evaporation of solvent and warmed at 55°C–60°C in a thermostatic water bath for 5-10 min with shaking until the ingredients were dissolved. In the final transparent solutions, distilled water added in this solution while warming in the water bath till a clear solution was obtained. Cooling of the solution formed a yellowish creamy preliposomal gel formed.

6) Spray drying method

Spray drying process is a continuous single step, allowing better control on particle size.

Spray drying is not only limited to aqueous solutions but also

used for non-aqueous solutions. Particles formed in spray drying are uniform size and shape are required and easily scaled up, cost effective and suitable for large scale production of Pre-liposomes.

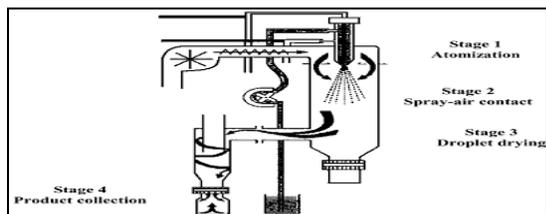


Fig 3: Apparatus for preparation of Preliposomes by Spray drying method [9]

Four stages of spray drying process:

- Atomization of the solution into a spray nozzle,
- Spray-air contact
- Drying of the spray droplets
- Collection of the solid product.

Liquid dispersions of drug, carrier, and lipid in organic solvent are prepared and pumped into the spray drying chamber. Spray drying process improved by optimizing the operating parameters such as drying inlet temperature, feed rate, and aspiration rate etc.

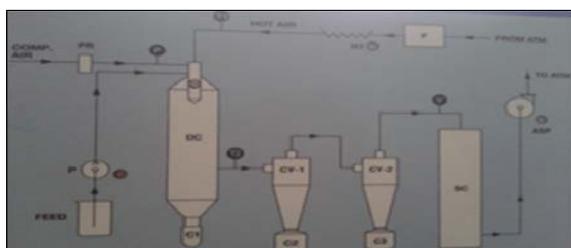


Fig 4: Flow chart of spray drying process

Spray drying is a method in which a fluid mixture usually being sprayed into a hot dry air. Spray drying can only be done, however, when the dried final product behaves as a non-sticky solid (not a liquid). The mixture being sprayed can be a solvent, emulsion, suspension or dispersion. It is atomized into millions of individual droplets by a nozzle. This process increases the surface area of the sprayed solution. The solvent is vaporized immediately by the hot air. This vaporization process rapidly removes heat so that the product is dried gently without thermally shocking it. The product is turned into a powder, granulate or agglomerate within seconds.

Characterization of Preliposomes

1. Formation of vesicular structures from preliposome powder

Small quantity of preliposomal powder was taken and placed on the glass slide add few drop of distilled water was added drop wise with the help of dropper and a cover slip was placed over it. The slide was placed under the inverted microscope, observed at a magnification of 450X formation of vesicular structures were seen (Nikon) and micrographs of the formed liposomes were taken.

2. Flow Property

The preliposomes powders is vital handling and processing operations because the dose uniformity and ease of filling into container are dictated by the powder flow property. Generally

three types of flow measurements can be used to evaluate the flow property of powder that is Bulk density, Tapped density, Angle of repose, Carr's index, Hausner's ratio.

3. Surface morphology

For surface morphological evaluation, the preliposome powder was hydrated with distilled water and agitated manually for 10-15 min, and the scanning electron microscopy or Transmission electron microscopy observed and photographed was taken.

4. Measurement of particle size and size distribution of liposomes

The preliposome powder were hydrated with 1 ml of aqueous media under continues stirring for 45 min, before 4 ml was added to dilute the liposomes. To remove the carrier from the mixture was centrifuged for 3 min at 400 rpm. The supernatant containing liposomes and untrapped drug was placed in a volumetric flask and diluted with media up to 10 ml. This liposomal suspension was used for particle size and zeta potential determinations.

5. Drug content

Drug content was estimated Equivalents of one dose of drug preliposome powder was weighed and vesicles were lysed with 5 ml of methanol by bath sonication for 15 min to solubilize the lipids finally make up the volume up to 10 ml with dissolution media. Aliquots were withdrawn and dilute up to minimum concentration was obtained. Drug content was calculated for using UV-visible spectrophotometer.

6. Entrapment efficiency

The Entrapment efficiency of hydrophilic drug was determined by the hydrating equivalents dose of drug preliposomal powder in 10 ml of distilled water. Aliquots of sample was taken in micro centrifuge tubes and followed by Refrigerated centrifugation at 25,000 rpm at -20°C for 20 min. The supernatant was separated, suitably diluted with solvent and the sample was analyzed by UV spectrophotometer. The absorbance was converted into drug concentration using standard curve.

The encapsulation efficiency was calculated as:

$$\% EE = \frac{(\text{Total drug} - \text{Untrapped drug}) \times 100}{\text{Total amount of drug added}}$$

For Lipophilic drug same procedure as above is followed, but the direct entrapped drug was found by dissolving the residue in the particular solvent.

$$\% EE = \frac{\text{Entrapped drug} \times 100}{\text{Total amount of drug}}$$

7. In Vitro Dissolution Study

In vitro dissolution study of preliposome powder was performed by different method as listed below.

- 1) USP Dissolution apparatus Type II
- 2) Drug release study using Franz diffusion cell and skin permeation studies
- 3) *In vitro* skin permeation studies have been carried out using dorsal skin of albino rabbit
- 4) Keshary-Chien diffusion cell
- 5) Cellophane dialysis membrane

8. Stability study

Stability testing is to provide evidence of the effect of time and the influence of a variety of environmental factor such as

humidity, light, temperature, on the quality of the formulation. It varies and enable storage condition, re-test period, and shelf-lives. The formulations were stored in glass vials covered with aluminum foil were kept at room temperature and kept in a refrigerator (4 °C – 8 °C) for 30 days. At definite time intervals (10,20 and 30 days), samples were withdrawn and hydrated with phosphate buffer pH 6.8 and observed for any sign of drug crystallization under inverted microscope. Samples were also evaluated for particle size, Drug content and entrapment Efficiency before and after storage for 1 month.

Application of Preliposomes for novel drug delivery system

Provesicular systems are provides drug carriers with greater chemical and physical stability drugs. Provesicular systems had been attracted by researchers for Oral, IV and TDDS of drug due to its non-toxicity and high penetration of lecithin/surfactants. Provesicular systems also used to prepare tablet, capsule, Dry powder inhaler for the drugs which having stability problem.

1) Parenteral Delivery

For parenteral preparation liposomes are prepared for that sterilization is very difficult. In pharmaceutical company mainly sterilization is done by γ -radiation, steam heat sterilization, aseptic area manufacturing and filtration sterilization. Steam sterilization at 121 °C not suitable for liposomal preparation, at high temperature, it may disturbed the structure of liposomes due to hydrolysis of the phospholipids. Preliposomes are suitable for parenteral drug delivery because it sterilized by dry heat without disrupt the liposomes and store in dry state due to that its chemical and physical stability get improved as compare to conventional liposomes.

2) Oral Delivery

Oral drug delivery is most convenient route for drug delivery, but liposomes are limited because of its unstable dosage form and stability problem shown in liposomes. Preliposomes are free flowing dry powder form having high stability and stable dosage form in the form of dry powder inhalers, tablet, and capsule form. Preliposomes get converted in to liposomes when contact with physiological fluid at the site of action e.g. Zaleplon, Exemestane, Isradipine, Vitamin-E Valsartan, Vinpocetine, Silymarin, Salmon Calcitonin, Glyburide, etc...

3) Pulmonary Delivery

Preliposomes having advantages for pulmonary drug delivery due to its high stability, small particle size, and phospholipid having high affinity to provide encapsulated drug to the lung tissue with high absorption and local action in the respiratory tract. Pulmonary drug delivery provide with help of inhaler

- 1) Dry powder inhalers
- 2) Pressurized metered dose Inhalers
- 3) Nebulizers

4) Mucosal delivery

Preliposome forms in situ liposomes inside the body at the site of action when contact with biological fluid. Lipids having high affinity for the mucosal membrane and non-toxic, non-irritant in nature. Liposomes having stability problem and leakage of drug this problem is overcome by preliposomes are dry free flowing powder are easy to store and high stability. Preliposomes are provides prolong release drug delivery for vaginal, nasal route and increases drug retention at the site of action e.g., metronidazole, Clotrimazol etc...

5) Transdermal delivery

In preliposomes phospholipid take a major part of component of the provesicular drug delivery system. Lipid enhance the penetration power, diffusion of drug though the skin and avoid first pass metabolism. It provide the sustained release dosage form of drug which having low half-life, poor solubility and improves bioavailability e.g. Aceclofenac, nicotine

Conclusion

Preliposomes are novel vesicular carrier having ability to overcome the instability issue associated with the vesicular drug delivery system. To developed a provesicular drug delivery system for the challenging drug for large scale-up and controlled release of the encapsulated drug. Preliposomes having high chemical and physical stability and easily commercially scale up. Preliposomes also alternative carriers for the transdermal drug delivery due to non-toxicity and high penetration of lipids. Preliposomes have significant for oral drug delivery in the form of tablets, capsule, dry powder for the various route of administration. The Preliposomes are forming liposomes in situ during the disintegration, erosion, present the novel drug delivery for the formulation of drugs with high potential for industrial manufacturing.

Table 1.1: Application of preliposomes drug delivery system in pharmaceutical field

Drug	Evaluation	Provesicular type	Composition
Preliposomes drug delivery systems to improving oral bioavailability			
Nicotine	<i>In vitro</i> skin permeation studies	Preliposomes	Span 60
Cromolyn	<i>In vitro</i> studies Caco-2 cell study Intestinal sac study in rat	Preliposomes beads	Cromolyn, PVP, isopropyl alcohol
Halofantrine	Ex vivo studies rats	Preliposomes	Span 60
Exemestane	<i>In vitro</i> studies and Ex vivo studies rats, Caco-2 cell line study	Preliposomes	Dimyristoyl Phosphatidyl glycerol
Preliposomes drug delivery systems for Nasal drug delivery			
Nicotine	In vivo studies	Preliposomes	Egg lecithin. Sorbitol
Isoniazide & Pyrazinamide	<i>In vitro</i> studies	Preliposomes DPI	Phosphatidylcholine
Propranolol	<i>In vitro</i> and in vivo study	Preliposomes	Sorbitol, lecithin
Preliposomes drug delivery systems for IV administration			
Adriamycin and adriamycinol	In vivo studies	Preliposomes	Egg lecithin
Preliposomes drug delivery systems for Increases dissolution of poorly soluble drug			
Fenofibrate	Dissolution enhancement	Preliposomes	Phospholipids
Teniposide	Solubility studies	Preliposomes	phospholipid, Bile salts

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