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Proliposomes as Pharmaceutical Drug Delivery System

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ABSTRACT
A bilayer of phospholipids makes up the microscopic vesicles known as liposomes, which are a revolutionary drug delivery system that releases drugs at a predetermined rate controlled by factors such as need, pharmacological characteristics, drug profile, physiological state of the body, etc. However, liposomes have poor stability issues, which makes storage a challenge.
Pro-liposomes (PLs) were found in 1986 to solve this issue. Pro-liposomes are granular, freely emulsifying products made of drug and phospholipid precursors that, when hydrated, transform into liposomes. This research examines several aspects of pro-liposomes, including their preparation process, evaluation, applications, and the possibility to be used for multiple routes of administration.
Keywords: Liposome; Pro-liposome; Carriers; Phospholipids; Cholesterol

I. INTRODUCTION

Dr. Alec D. Bangham, a British haematologist, originally described liposomes in 1961 at the Babraham Institute in Cambridge. Greek terms "Lipos" (fat) and "Soma" (body) are the origin of the word "liposome" [1]. Liposomes are the most widely used, well-researched, and efficient new drug delivery method [2]. The term "liposome" refers to a tiny, spherical vesicle with an aqueous inside encased in phospholipid molecules. Drug compounds may be integrated into the lipid bilayer or the aqueous phase. They are frequently employed as a means of delivering nutrients and pharmaceutical medications in order to lessen their negative effects and increase the stability and efficacy of the drug [3]. Before reaching the intended site to exert therapeutic action, Liposomes must be stable and undamaged both during the storage period and before being released onto the market. Liposomes are relatively unstable colloidal structures, nonetheless, because of their physical and chemical instability [4]. In order to address the stability problem with liposomes, a new "pro-liposome" approach has been devised that can swiftly create liposomes on demand and with minimal manipulation [5]. Liposomal solution may have a short shelf life. In 1986, pro-liposomes (PLs) were found [6]. Pro-liposomes are granular, dry items that flow freely when they come into touch with biological fluids in the body or when they are moistened. They are made up of phospholipid and porous powder that is water soluble [7].

The Pro-liposome process is one of the most popular and economical ways to make commercial liposome products. They are accessible in dry powder form, which makes them simple to transfer, measure, and store. This makes the system versatile. Before being administered, liposomes can either be created in vitro using an appropriate hydration fluid or in vivo under the effect of biological fluids in the body [8]. Creating pro-liposomal formulations can solve many medications' solubility and bioavailability issues [9].

II. CHARACTERIZATION OF PRELIPOSOMES

1. Vesicular structure formation from preliposome powder- A small amount of preliposomal powder was taken and placed on a glass slide. A few drops of distilled water were added drop by drop. Vesicular structure formation was observed at a magnification of 450X using a Nikon camera, and micrographs of the formed liposomes were taken.
2. Flow Property - The preliposomes powders are essential for handling and processing procedures because the powder flow property determines the dose uniformity and simplicity of filling into containers. In general, three different flow measurements—Bulk density, Tapped density, Angle of repose, Carr's index, and Hausner's ratio—can be used to assess the flow attribute of powder.
3. Surface morphology - To assess the surface morphology, the preliposome powder was hydrated with distilled water and stirred manually for 10 to 15 minutes. Particle size and zeta potential were

then determined by scanning electron microscopy or the liposomal solution.

4. Drug content was examined using transmission electron microscopy, and photos were taken. mixture was centrifuged at 400 rpm for three minutes. The unentrapped medication was put in a volumetric flask with the supernatant ml of aqueous media under continuous stirring for 45 minutes, before 4 ml was added to dilute it with medium up to 10 ml. Measurement of particle size and size distribution of liposomes-

One liposome was used to hydrate the preliposome powder. The projected cost of separating the drug substance from the carrier Preliposome powder equivalents of one dose were weighed, and vesicles were lysed in 5 ml of methanol by bath sonication for 15 min. to solubilize the lipids before being filled with dissolution media to make the volume up to 10 ml. Aliquots were taken out, and the minimal concentration was attained by dilution. Utilizing a UV-visible spectrophotometer, drug content was estimated.

5. Entrapment efficiency.

The hydrating equivalents sample dose of drug preliposomal powder in 10 ml of distilled water was used to calculate the entrapment efficiency of hydrophilic drugs. Aliquots of were placed in tiny centrifuge tubes, and then they underwent 20 minutes of chilled centrifugation at 25,000 rpm at -20°C. The material was separated, appropriately diluted with solvent, and subjected to UV spectrophotometer analysis. The absorbance was converted into drug concentration using

The encapsulation efficiency was calculated as:

% EE = (Total drug-Unentrapped drug) X 100 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 = Entrapped drug X 100 Total amount of drug

6. 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

7. Stability study -

The purpose of stability testing is to demonstrate how the quality of the formulation is affected by time and a number of external factors, including humidity, light, and temperature. It varies and facilitates shelf lives, re-test intervals, and storage conditions. For 30 days, the formulations were kept in refrigerators (4–8 °C) and at ambient temperature in glass vials covered with aluminium foil. At predetermined intervals (10, 20 and 30 days), samples were removed, hydrated with phosphate buffer pH 6.8, and examined under an inverted microscope for any indication of drug crystallisation. Before and after being stored for a month, samples were also assessed for particle size, drug content, and entrapment efficiency.

III. FACTORS EFFECTING PROLIPOSOME FORMULATION

1) Total lipid concentration: As the lipid concentration grew, so did the drug's % encapsulation efficiency. As a function of total lipid concentration, the percentage encapsulation efficiency of the medication increased linearly.

2) Drug concentration: Preliposomes with higher drug concentrations demonstrated improved encapsulation efficiency and drug content per mole.

3) Charge of the lipids: The percentage of drug encapsulation efficiency was reduced when dicetyl phosphate (DCP), which creates a negative charge, or stearylamine (SA), which induces a positive charge, was added to the lipids.

4) Effect of Phosphatidylcholine (PC) -to-Cholesterol Ratio;

The percentage drug entrapment efficiencies of preliposomes can be generated at different amounts of phosphotidylcholine (PC) to cholesterol, which shows that incorporation of more cholesterol would result in greater EE (%) at a constant molar ratio range. One of the key considerations in the creation of proliposomal preparations and liposomes is the cholesterol content. Although cholesterol can be incorporated into phospholipid bilayers, it does not actually form the bilayer structure by itself. Cholesterol may be injected into the membrane because it is amphipathic, with the hydroxyl group facing the aqueous surface and the aliphatic chain positioned parallel to the acyl chains in the middle of the bilayer. However, when the cholesterol content exceeds a certain level, it may reduce the partitioning of drug molecules to the bilayer membrane, resulting in a reduction in the degree of

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encapsulation. As can be observed, the increasing cholesterol concentration was shown to greatly improve the entrapment efficiencies of all proliposomal formulations. The rigidifying action of cholesterol in the fluid crystal state, which facilitates the entire creation of the vesicles with respect to the bilayer membrane, may be responsible for the enhancement in entrapment efficiency. Without this impact, the degree of encapsulation would decrease. As can be observed, the increasing cholesterol concentration was shown to greatly improve the entrapment efficiencies of all proliposomal formulations. There may be several causes for cholesterol's increased impact on entrapment effectiveness.

5) Effect of total lipid-to-sorbitol ratio: According to a comparison of total lipid:sorbitol ratios between 1:10 and 1:20, the concentration of sorbitol has no appreciable impact on the EE% of CT. However, when the total lipid-to-sorbitol ratio is more than 1: 10, it is challenging to prepare the preliposomes from a preparation standpoint. The spraying-evaporating procedure takes substantially longer because only a very small volume of the solution of membrane-forming components can be injected and sprayed onto the small amount of sorbitol at a time. A 1: 10 sorbitol concentration was employed to manufacture the proliposome because a larger sorbitol concentration did not enhance the formation.

IV. METHOD OF PREPERATION

(PLs) are prepared by many methods such as:

- Film-deposition on carrier method
- Spray drying method
- Fluidized-bed method
- Supercritical anti-solvent method

Film depsition on carrier method

Pro-liposomes are made using the film deposition on carrier technique. In this process, a permeable, water-soluble carrier material is used to discharge the medication and phospholipid coat. As seen in Figure 1, a feed tube drops an evaporative solution containing a medication and phospholipid solution onto a carrier substance core that is carried in a vessel of a rotating flash evaporator under vacuum. When a free-flowing powder matrix is obtained, the overwetting of the matrix is avoided at any given time and the subsequent aliquot of organic mixture is only fed [10]. To control the amount of carrier that is required to support the lipids, chosen carriers should have a large surface area and permeability. Additionally, this enables the creation of pro-liposomes with a high surfactant to carrier mass proportion. They may quickly produce liposomal dispersion upon hydration due to their water solubility, and by carefully controlling the size of pervious powder, a relatively small range of reconstituted liposomes can be obtained. Maltodextrin, sorbitol, microcrystalline cellulose, magnesium aluminium silicates, mannitol, and other substances are the most often utilised carriers [11]. Slow incorporation and evaporation steps of the solvent [12]. Change the process by spreading the carrier substance in an organic medicine and phospholipid mixture in a rotary evaporator vessel before sending it to vacuum evaporation to get around this problem. This results in highly ordered and constant lipid dispersion and a stable procedure that takes less time than the real procedure [13]. method of spray drying This process' reclining propensity is what makes it unique.

Pro-liposomes are made via a film deposition process on a carrier. In this process, the medication and phospholipid coating is released onto a permeable, water-soluble carrier material. A feed tube injects an evaporative solution containing a medicine and phospholipid solution drop by drop onto a carrier substance core that is contained in a vessel of a rotating flash evaporator under vacuum. The matrix's overwetting is avoided at any given time, and the subsequent aliquot. To control the amount of carrier that is required to support the lipids, chosen carriers should have a large surface area and permeability. Additionally, this enables the creation of pro-liposomes with a high surfactant to carrier mass proportion. They may quickly produce liposomal dispersion upon hydration due to their water solubility, and by carefully controlling the size of pervious powder, a relatively small range of reconstituted liposomes can be obtained. Maltodextrin, sorbitol, microcrystalline cellulose, magnesium aluminium silicates, mannitol, and other substances are the most often utilised carriers [11]. Slow incorporation and evaporation steps of the solvent [12]. Change the process by spreading the carrier substance in an organic medicine and phospholipid mixture in a rotary evaporator vessel before sending it to vacuum evaporation to get around this problem. In contrast to the actual technique, this results in a stable and less time-consuming lipid dispersion that is very consistent and well-organized [13].

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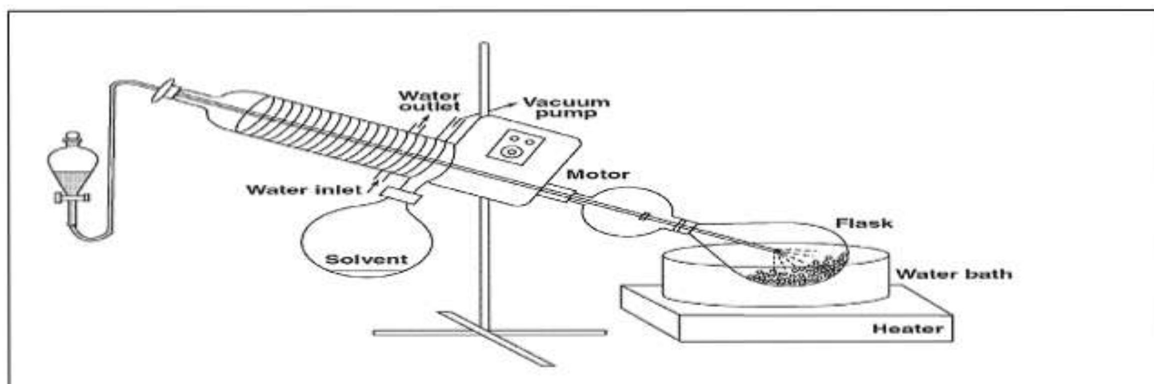
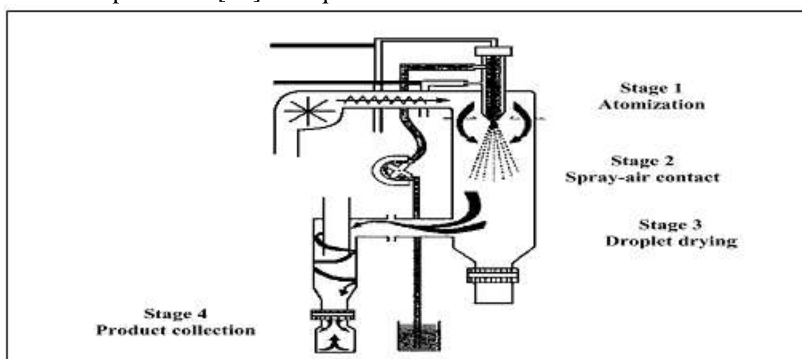


Apparatus for Preparing PLs by film deposition on carrier method

Spray drying method

It allows for more acceptable particle creation by combining particle composition and drying in a uniform manner. Any aqueous or non-aqueous system for producing particles can use this technique. This method is typically used when uniformly sized and shaped particles are required and may be easily scaled up. For the extensive preparation of PLs, its pricing is efficient and reasonable [14,15]. Figure 2 illustrates the four stages of the spray drying process: product atomization into a spray nozzle, spray-air association, drying of the spray droplets, and collecting of the solid product [16]. Liquid dispersions containing pure lipids or lipids and carriers in an organic combination are first prepared, and then they are put into the dry cell. Dispersions are atomized into drying cells using a spray nozzle and desiccated in a simultaneous air flow that is subsequently collected in a tank [16]. High temperatures, shearing stresses, and absorption episodes are the main issues affecting this approach since they can cause active molecules to degrade mechanically and thermally. By improving the working variables, it can be improved. Examples of working variables are drying air temperatures and liquid spraying rate.



Appratus for preparing PLs by spray drying method

Supercritical anti-solvent method

Supercritical Carbon Dioxide (SCCO2), which is actually carbon dioxide's fluid state when it is maintained at some degree above its critical temperature and pressure, is used in the Super Critical Anti-Solvent Method for the Production of PLs. Because of three primary factors: lower residual solvents, straightforward procedures, and mild operating temperatures. To create PLs, we employ anti-solvent technology. In those straightforward processes, a three-part equipment (such as a sample delivery unit, a precipitation unit, and a separation unit) is typically employed. Two pumps are used: one to deliver CO2, which is delivered through a CO2 cylinder (72 cm3) and then introduced to a buffer tank (-7°C) for preheating using a high pressure pump. One for the drug solutions that is introduced by HPLC pump combines up to form the sample delivery unit, and the conditions of the reaction vessel or CO2 cylinder should be 45°C and 10 MPa [17]. To dissolve the medications, a solvent that is entirely miscible with CO2 should be employed. Phospholipids, cholesterol, and medication were

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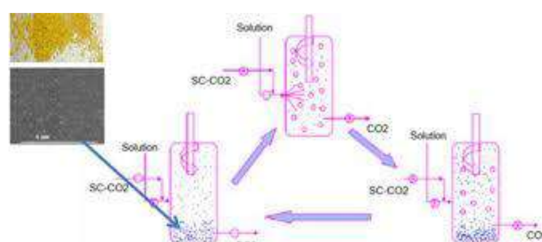
dissolved in organic solvents for both formulations, and then the mixture was sonicated until it was uniformly transparent. The nozzle valves A and B will be opened to allow CO2 to enter the vessel. The inside tubule of the nozzle is used to spray the solution, while the outside tubule is used to spray CO2. The heated by air bath vessel makes up the device' second component, while a separator and a wet gas metre make up its last component. Due to its low pressure, SCCO2 is separated from organic solvent in the last part's separator, and CO2 is measured using a wet gas metre [18]. When the temperature and pressure reach the specified levels, valve A opens to let CO2 in, and then valve B opens to let the medication solution go into the nozzle. Rapidly, the solution and SCCO2 are combined and dispersed into one another as though through a coxial nozzle. Due to the solute's gradual decline in solubility in the organic solvent, which causes the PLs to precipitate in the vessel, the solute will dissolve in the organic solvent to approach supersaturation in a matter of around 30 minutes. We collect these samples at the bottom of the vessel on the filter after the solution has been fully utilised. A and B valves are closed, and valve C is opened to depressurize the vessel at the opening temperature. To achieve high drug loading PLs, the pressure, temperature, and flow rate of the drug solution must be tuned.

Fluidized bed method

PLs are produced on a wide scale using particle coating technology, and the carrier material used can range from crystalline powder to non-pareil beads. When employing non-pareil beads as a carrier material, non-pareil beads are first coated with seal coating to provide a smooth surface. This coating can then be used to help coat phospholipids and ensure thin, homogeneous coating formation around the core and small-sized liposomes upon hydration. Then, through a nozzle, the drug and organic solvent solutions are sprayed onto the carrier material, and the organic solvent is eliminated from the fluid bed by simultaneously applying suction. The resulting lipid-coated powder removes the minute quantity of left over solvent.
Advantages include; beads when dried under vacuum overnight (Figure 3).

- Well establish and processable Film corating technology
- Number of various ways of coating
- Cost effective method [19,20].



Fluidized bed method

V. EVALUATION OF PROLIPOSOME

- Scanning electron microscopy
- Transmission electron microscopy (TEM)
- Hydration study
- Zeta potential
- Flow property

1. **Scanning electron microscopy (SEM) -** It is employed to examine the PL powder's surface structure. It provides a comparison of the liposome's picture with that of pure carrier substance. Proliposomes' formulation is confirmed by the carrier material in the formulation, which also confirms the phospholipids' arrangement on the carrier [21].
2. Transmission electron microscopy (TEM) - This technique is also utilised to examine the liposome structure following hydration of PL powder. In this procedure, the proliposome powder is hydrated with distilled water before being examined under a microscope to determine the lamellarity and morphologies [8,10,21]. This procedure continues until the carrier's breakdown and the hydration of the lipid layer are complete [22].
3. Zeta potential - The zeta potential can be used to calculate a particle's surface charge. It is the potential difference between the solution's electro-neutral area and the tightly bonded layer's surface (shear place) [23].
4. Flow property - The flow property of a powder formulation can be used to explain content uniformity and managing processing operations. Analyzing the pro-properties liposome's is important for a formulation based on solid powder.

The metrics Angle of repose, Carr's Index, and Hausner's ratio can be used to evaluate it [11,22].
5. Hydration study - Based on the discovery that liposomes are created when they come into contact with an aqueous environment. In this technique, we first add a little amount of dry pro-liposome powder on a glass slide, add water to it gradually, and then use a microscope to visualise the vesicle.

VI. APPLICATIONS

Pro-liposomes can be formulated for the below mentioned routes of administration.

Parenteral delivery

For parenteral application, most important is their sterilization. Sterilization techniques commonly used are steam sterilization, γ-irradiation, aseptic manufacturing and filtration sterilization. Terminal sterilization is not appropriate for liposomal formulations as it requires steam at 121°C. At high temperature liposome structure is destroyed because of lipid hydrolysis and boosts the per oxidation of unsaturated lipids [10-11].

Oral delivery

Pro-liposomes help to enhance the dissolution efficiency of poorly soluble drugs. It produces multi-lamellar vesicles on contact with fluid which guarantees higher entrapment of insoluble drugs due to widened hydrophobic volume within the liposomal lamellae. It also permits conversion of drug from crystalline to amorphous form. Improvement in bioavailability of drugs having extensive first pass metabolism and increased lymphatic uptake is due to larger particle size of multi-lamellar liposomes formed on hydration [12].

Pro-liposomes are formulated to increase stability of liposomes. Formulations improve solubility and bioavailability of some poorly soluble drugs. Domperidone is a specific 5HT3 receptor antagonist used as anti-emetic. Domperidone is poorly soluble in water and after oral administration it undergoes extensive gastric and hepatic first pass metabolism. Due to its extremely low oral bioavailability, this prevents it from having the desired therapeutic impact..Domperidone pro-liposomes are created to boost bioavailability by improving intestinal permeability that results in improved lymphatic uptake and circumventing first pass metabolism.

Pulmonary delivery

Liposomal preparations are also formulated for localized drug action in the respiratory tract. As liposomes are composed of phospholipids that are also a part of lung surfactant thus, drug entrapment within the liposomes result in improved absorption. Drugs encapsulated in Liposome are present in blood for extended period of time and with decreased adverse effects [13].

Mucosal delivery

Pro-liposomes on contact with aqueous mucosal surfaces transformed into liposomes. Phospholipids are the component of pro-liposomes which are non-toxic, non-irritant and compatible with biological membranes. The molecular dispersion of drug into bilayer results in increased therapeutic action [14].

Transdermal delivery

Pro-liposomes are composed of phospholipids that have natural affinity for skin lipids and thus enhance the drug permeation within the skin. Pro-liposomes on hydration are converted to liposomes that lead to sustained action of entrapped drug. Liposomes developed on contact with aqueous environment regulate diffusion across the skin. Hence the permeation of skin is increased by avoiding the stratum corneum hindrance [15-16].

Ocular drug delivery

Conventional ocular drugs have poor bioavailability because of precorneal loss effects. Pro-liposomes are used to enhance the drugs bioavailability and their therapeutic action. Drugs entrapped within the lipid bilayer of liposomes have high solubility and can traverse cornea. Liposomal formulations can easily be used for ocular drug delivery. Liposomal hydrogels of Ciprofloxacin are used in order to prevent catheters from bacteria [16].

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