LIPOSOMAL DRY POWDER : AS A NOVEL CARRIER OF PULMONARY TARGETED DRUG DELIVERY SYSTEM

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Abstract: Liposomal dry powder inhalers (DPIs) are emerging as a promising strategy for targeted pulmonary drug delivery, combining the benefits of liposomal drug carriers with the advantages of dry powder formulations. Nebulization of liposomal powder provides target drug delivery. These systems offer enhanced drug stability, controlled release, and reduced systemic side effects, making them ideal for treating various lung diseases. The main objective of that review to investigate different formulation techniques methods such as Sonication, French Pressure Cell, Reverse Phase Evaporation, Lyophilization, Thin-Film Hydration, Ether-Ethanol Injection, Micro Fluidization and Supercritical Fluid Technology show potential, depending on the specific formulation requirements. Among these methods, Spray Drying is the most widely employed due to its scalability, simplicity, and ability to produce particles with optimal aerodynamic properties for deep lung deposition. These approaches contribute to improved particle size control, drug loading efficiency, and product stability. As formulation science advances, the focus remains on optimizing these technologies to ensure consistent performance, safety, and therapeutic efficacy in clinical applications.

Keywords: Liposomes, Spray drying, Microflidization ,Lyophilization, Thin film hydration.

1 INTRODUCTION

Liposomes are concentric bilayered vesicles in which an aqueous volume is totally encased by a membranous lipid bilayer composed primarily of characteristic or manufactured phospholipids. The structure of a liposome vesicle is appeared in Fig.1.1. Liposomes are the commonly utilized lipid-based sedate conveyance frameworks, other lipid carriers being strong lipid nanoparticles (SLN), sleek suspensions, submicron lipid emulsions, lipid inserts, lipid microtubules, and lipid microspheres. Liposomes are naturally congruous, biodegradable, and non-toxic structures as these are arranged from phospholipids display in the pneumonic surfactant. Liposomes can carry both hydrophilic and lipophilic drugs. Besides, these can effectively and systemically convey cytotoxic, anti-asthmatic, anti-microbial. The chosen excipients utilized in pro-liposome generation are known to influence not as it were the medicate discharge profile but moreover the aerosolization execution. Phospholipids are the building piece of liposomes, which are microspheres. They give supported medicate discharge, hold sedate particles, and work as a slow-release reservoir. A lipid sandwich envelops the liposomes' aqueous compartments compared to Liposomal formulations, among other medication forms, restrict the entry of the medication into the bloodstream, enabling the medication to must be equally distributed across the airways of the lungs. They result in a decrease in the frequency of medication doses. They greatly improve life quality and reduce medical costs. To develop a very effective method for when administering pulmonary drugs, dry powder inhalers need to be thoughtfully put together. The aqueous liposomal dispersions because of its volatility its dry powder form is more useful for administration. Many investigations on liposomal formulation resulted in to the hypothesis that liposomal particles exhibit regulated additionally.

1.1 Structure Of Liposome

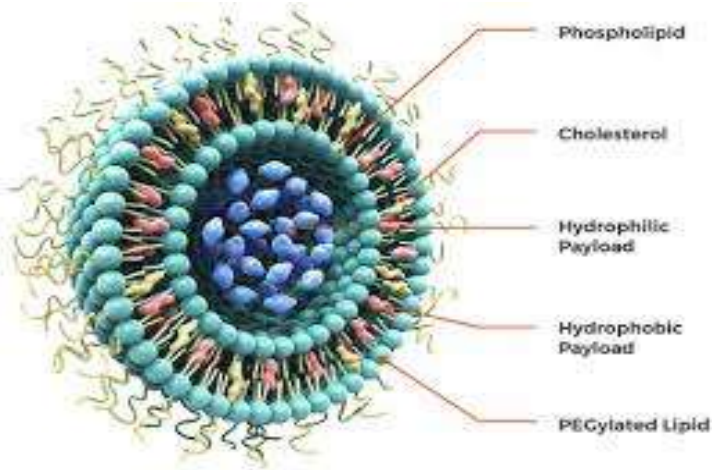


figure. 1.1 structure of liposome

Liposomes are microscopic vesicles composed of the same substance as a cell membrane. They can be loaded with medication and used to administer medication for a number of serious illnesses, including tuberculosis and cancer. Liposomes extend the residence time of encapsulated medicines for a longer duration and promote intracellular drug delivery. Greek terms "Lipos," which means fat, and "Soma," which means body, are the source of the word "liposome." Liposomes are micro spherical, colloidal, bi-layered vesicles with an aqueous core surrounded by phospholipid molecules. It may have benefits such as allowing active medications to be directed to the appropriate site of action and encapsulating both hydrophilic and hydrophobic medicines inside liposomal vesicles. These carriers have a size range of roughly 0.01 to 5.0 µm. When the phospholipids are more hydrated than the aqueous media, liposomal vesicles are generated.

1.2 Types of Liposomes

Table 1 Types of Liposomes

Types of Liposomes	Size Range
Small Unilamellar Vesicle (SUV)	20-100 nm.
Large Unilamellar Vesicle (LUV))	>100 nm.
Giant Unilamellar Vesicle (GUV)	>1000 nm.
Multilamellar Vesicle (MLV)	>0.5 um.

Liposomes are normally characterized by their size and lamillary; however, they can also be categorized into one two groups.
A. Unilamellar Vesicles: In unilamellar vesicles, the vesicles have a single phospholipid bilayer sphere enclosing the aqueous solution.

- Small Unilamellar Vesicles (SUV): 20-100 nm : They are single layered liposome clearance from the systemic circulations reduced and hence they circulate for long.
- Large Unilamellar Vesicles (LUV): >100 nm: They vary in size from around 100 nm to 10 micrometres in diameter and a greater number of drugs can be encapsulated. But they are more fragile.
- Giant Unilamellar Vesicles (GUV): >1000 nm: They are single layered liposome clearance from the systemic circulations reduced and hence they circulate for long.

B. Multilamellar Vesicles: It is also called as multi-vesicular vesicles and vesosome. In multilamellar liposomes, this consists of numerous concentric bilayers, alternating with layers of water. The advantage of MLV is that they are simple to make and have a rugged construction. But only a small percentage of drugs can be encapsulated. It is rapidly cleared from the blood and hence is used in passive targeting of the liver and spleen.

1.3 Liposomal Pulmonary Drug Delivery

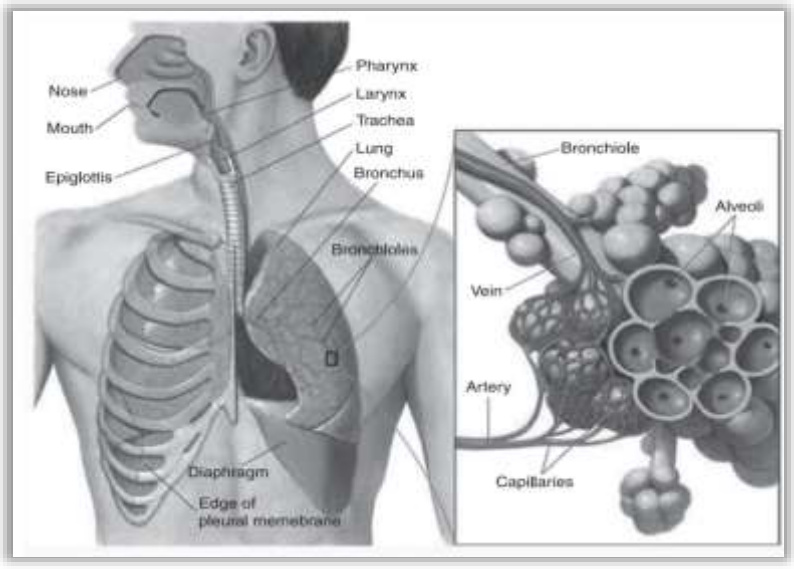


figure.1.2 pulmonary drug delivery system

The effectiveness of an inhaled medication is determined by its ability to pass through the lung epithelial barrier and reach its pharmacological site of action. Locally active drugs that are absorbed into the systemic circulation may be eliminated from the body, which would stop the drug's effect in the lungs. The way that a drug is absorbed from the lungs affects the systemically acting medications duration, potency and start of action. Despite being a tried-and-true way of administering medication, inhalation, the kinetics of drug absorption in the lungs have not been well investigated. For the purpose of creating novel inhalation products with both local and systemic effects, it is essential to comprehend the variables influencing the absorption and disposition of inhaled medications regarding their molecular properties. The purpose of respiratory host defense has been to keep airborne particles and possible pathogens out of inspired air. The system is made up of chemical defense mechanisms, air filtration, coughing, sneezing, and mucociliary clearance, as well as antioxidants, surfactant fats, and antiproteases. It is strictly controlled to reduce inflammatory reactions. Due to its suitability for drugs with local effects in the lung, such as those used to

treat asthma, chronic obstructive pulmonary disease, respiratory distress syndrome, pulmonary infections, and cystic fibrosis, the pulmonary route of drug delivery offers significant advantages over other methods. This is because it allows for a rapid onset of therapeutic action.

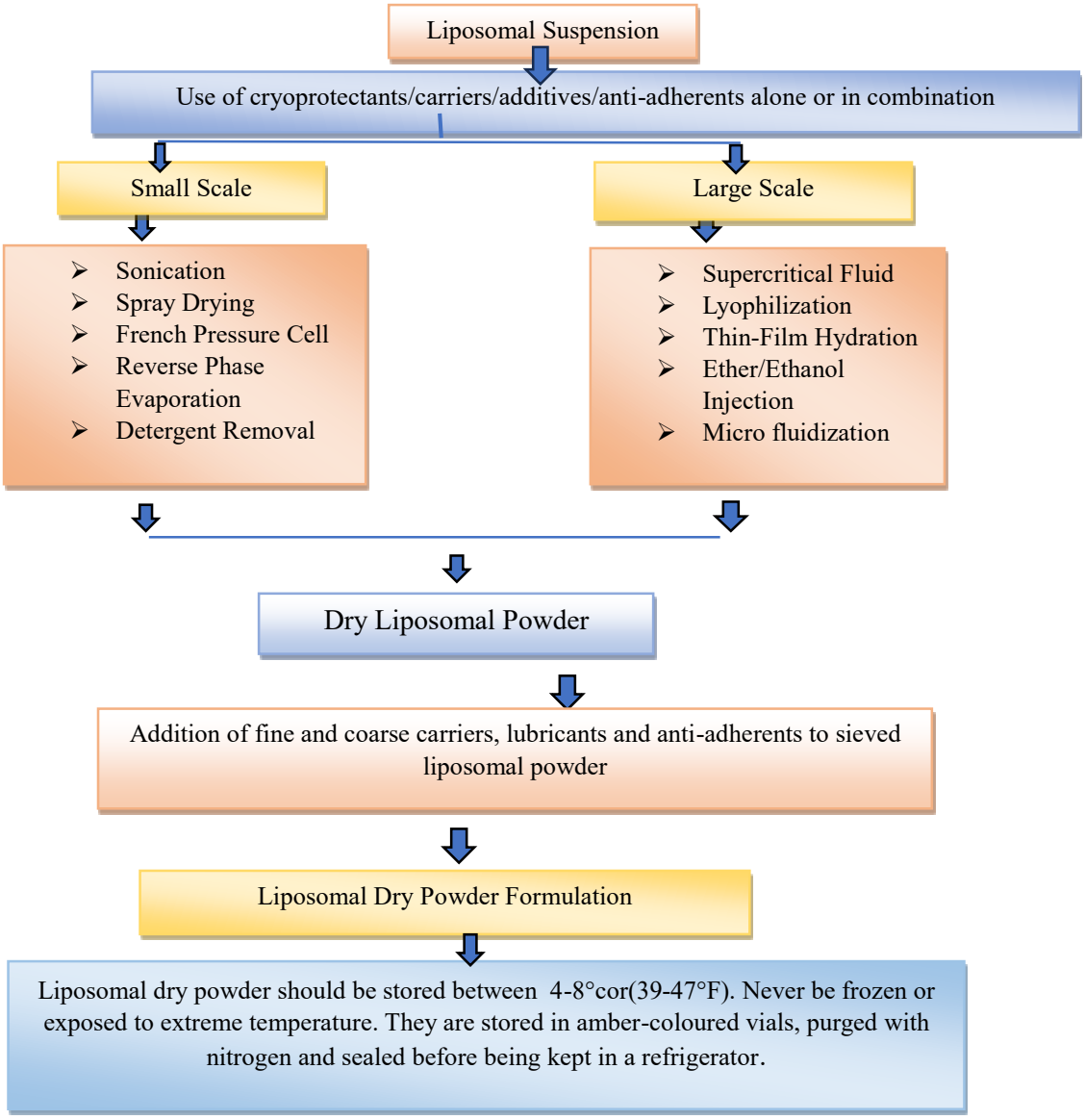
2. LIPOSOMAL DRY POWDER INHALER

Conventional liposomal DPIs are prepared as either loose agglomerates of micronized drug particles with a particle size of less than 5 mm or as carrier–drug mixes comprising micronized drug particles adhering onto the surface of large lactose carriers. The creation of liposomal suspensions, on the other hand, is a current trend in LDPI formulation. These suspensions are subsequently dried liposomal powders through the use of supercritical fluid technology, lyophilization, spray drying, spray freeze-drying, and cryoprotectants, either separately or in combination. Lubricants and anti-adherents are added to the liposomal dry powder obtained coarse carriers, and the mixture is then sieved to produce the final liposomal dry powder formulation. Recent research has indicated that DPI technology is successful in delivering liposomal medications to the lungs. The hypoglycemic potential of insulin-loaded liposomes that were spray-freeze dried and administered by DPI to rats. By using the reversed-phase evaporation process, insulin liposomes were created, and the resulting liposomal suspension was spray-freeze dried. Insulin-loaded liposomes were administered to rats intratracheally and this resulted in a decrease in their blood glucose levels. Compared to the outcome of insulin solution administration, this effect persisted noticeably longer. With improved stability and medication control, a liposomal powder for respiratory aerosol delivery made with lung endogenous surfactant phospholipid-like offers a special possibility in pulmonary quantum medicine. The pulmonary route presents many benefits for the delivery of LDPI, including regulated size production, sustained release, prolonged retention in the lungs, biocompatibility, and improved bioavailability. Drugs targeted as nanoparticles show promise for better lung cancer treatment, and a combination of medication targeting and respiratory therapy is even more successful in treating this type of cancer. One new inhalation therapy combination that may be even more precise and target-oriented for site-specific distribution is the use of DPI made of liposomes. An aerosolized liposomal powder for respiratory administration.

Table.2.1. Active Pharmaceutical Ingredient used in Liposomal Dry Powder Inhaler.

Active Pharmaceutical Agent	**Category**
Curcumin, Doxorubicin, Gemcitabine Hcl, Afatinib, Vinblastine sulphate.	Anticancer.
Fluconazole, Amphotericin B, Clotrimazole.	Antifungal, Parasitic Pulmonary Infection.
Amikacin, Mafenide acetate.	Antibiotic
Tacrolimus, Sirolimus.	Immunosuppressive Drugs.
Acetazolamide, Brimonidine tartrate.	Ophthalmic.
Nimesulide, Ketorolac tromethamine.	Analgesic.
Colchicine, Budesonide.	Idiopathic Pulmonary Fibrosis.
Andrographolide.	Anti-Inflammatory, Pneumonia.
Salbutamol Sulfate.	Asthma.
Fasudil, Afatinib, Erlotinib	Pulmonary Hypertension.

3. LIPOSOMAL DRY POWDER FORMULATION METHOD



3.1. SMALL SCALE FORMULATION METHOD

3.1.1. Sonication

The sonication process, which uses sonic energy in an inert atmosphere such as nitrogen or argon, is based on size transformation and entails sonicating MLVs that have been created using the thin-film hydration method. Using a bath-type or probe-type sonicator, the sonication approach allows for the homogeneous dispersion of tiny vesicles with the potential for increased tissue penetration. The lipid suspension receives high energy delivery from the probe tip sonicator. Degradation is brought on by the potential for the lipid solution to overheat. Prior to use, titanium particles that are released by sonication tips into the lipid mixture must be extracted by centrifugation. The bath sonicator are the most extensively used apparatus for preparation of SUV. They are applied to huge volumes of lipids that are diluted. The primary disadvantages of the approach include the oxidation of unsaturated bonds in the phospholipid's fatty acid chains and hydrolysis into lysophospholipids and free fatty acids, as well as the denaturation of compounds that are thermolabile and the extremely poor internal volume encapsulation efficiency.

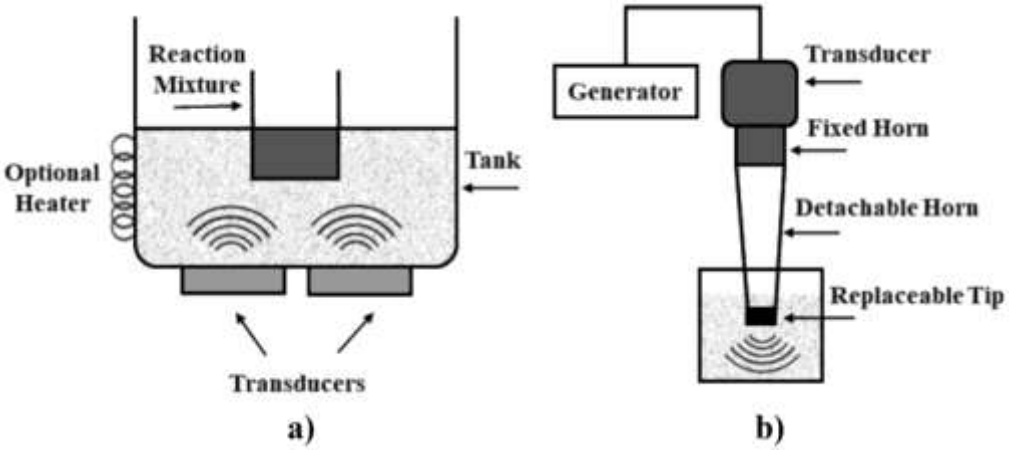


figure.3.2 sonification

- **Probe Sonication:** The liposome dispersion is immediately in contact with the sonicator's tip. This approach has a very large energy input for lipid dispersion. The vessel needs to be submerged in an ice or water bath because the coupling of energy at the tip causes local heat. Up to one hour of sonication is sufficient to deesterify over five percent of the lipids. Titanium will also flake off and contaminate the fluid while using the probe sonicator.
- **Bath Sonication:** The cylinder containing the liposome dispersion is put inside a bath sonicator. When employing this method instead of sonication by dispersal directly using the tip, temperature control over the lipid dispersion is typically easier. The substance that is being sonicated may be shielded by an inert environment, a sterile vessel, or something else entirely.

3.1.2. Spray Drying

One of the most widely utilized methods for creating powders that flow freely from liquids is spray drying. The result of spray drying is uniformly shaped and porous particles, which is useful for inhalation therapy in particular. Technical factors such as the starting solution's characteristics, the drying fluid's temperature, and the dried particle's movement speed can all be managed to change the morphology of the particle. Four steps can be used to summarize the procedure: The prepared solution is first atomized in the drying chamber using a spray nozzle with the necessary features. The second is the interaction of the atomized particles with the drying chamber's heated air. Third: two processes of drying the produced particles. Initially, the solvent evaporates from the solution until a high particle concentration is reached at the surface, creating a layer that resembles crust. The temperature of the particles stays almost constant. According to this, additional heating causes the temperatures of the particles to significantly rise, which in turn causes the solvent residues to be removed by diffusion via the pores in the crust-like layer. The gathering of the dried particles from the settling tank is the fourth step. In comparison to other methods, the process is less expensive and simpler. Because of the evaporating gas's cooling impact, which balances the drying gas's high temperatures, it can be employed with thermolabile pharmaceutical.

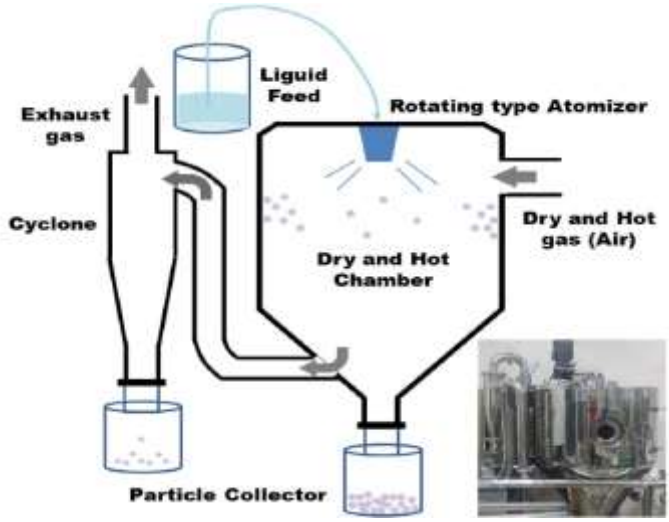


figure.3.3 spray drying

Spray drying offers more control over molecule arrangement and is subsequently a more appropriate approach for creating micron-sized powders for pneumonic organization. This makes it simple to exchange to large-scale generation. LDPIs were already made by shower drying utilizing cosolvent frameworks, which were generally composed of an aqueous/organic dissolvable or a combination of fluid and natural solvents, or by single and/or numerous emulsion strategies. Since the dynamic fixing is truly drying at room temperature, warm debasement of the chemical is not a genuine concern. There have been reports of splash drying ethanolic arrangements containing anti-asthmatic medicines and sedate carriers. To survey the respirable qualities, superoxide dismutase was typified in the spray-dried liposomes.

3.1.3. French Pressure Cell

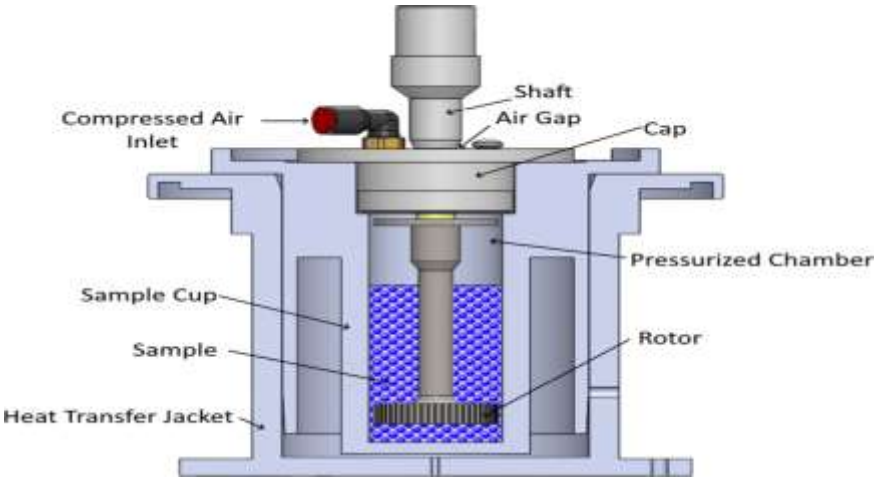


figure.3.4 french pressure cell

MLVs are expelled through a little opening at 20,000 psi and 4°C utilizing the French weight cell strategy. Compared to the sonication prepare, this approach is clearer and more repeatable, which is fair one of its various benefits. It moreover involves taking care of unsteady materials with care. Utilizing this procedure, impressively bigger liposomes than sonicated SUVs are made. The method's deficiencies are its moderately working volumes and its trouble in controlling the perfect temperature. MLV is expelled through a little opening in a French weight cell. The truth that the proteins do not show up to be essentially modified all through the handle as they are in sonication is a key component of the French press vesicle approach. An interesting perception is that, when captured solutes are made by sonication or cleanser expulsion, French press vesicles appear to keep in mind them distant longer than SUVs. Compared to the sonication approach, the strategy has a number of preferences. Bigger than sonicated SUVs are the resultant liposomes. The method's deficiencies incorporate its moderately humble working volumes (most extreme of 50 mL) and its trouble in keeping up the tall temperature.

3.1.4. Reverse Phase Evaporation

Since it made it conceivable to make liposomes with a tall watery space-to-lipid proportion and the capacity to capture a critical parcel of the watery fabric advertised, this strategy progressed the science of liposomes. The arrangement of modified micelles is the establishment of reverse-phase evaporation. The arrangement of these rearranged micelles happens through the sonication of a blend counting a natural stage that solubilizes the amphiphilic atoms and a buffered fluid stage that contains the water-soluble atoms to be typified into the liposomes. The continuous expulsion of the natural dissolvable causes the rearranged micelles to alter into a gooey state and in the long run gel. The gel state collapses at a significant arrange in this prepare, and a few of the rearranged micelles were conveyed. Liposomes are created when there is a wealth of phospholipids in the environment, which makes a difference to construct a full bilayer around the remaining micelles. Compared to hand-shaken or multilamellar liposomes, turn around stage vanishing liposomes have a watery volume-to-lipid proportion four times higher and can be created from an assortment of lipid definitions. In brief, the water-in-oil emulsion is shaped by briefly sonicating a two-phase framework that contains phospholipids in a natural dissolvable, like diethyl ether, isopropyl ether, or a combination of chloroform and isopropyl ether with watery buffer.

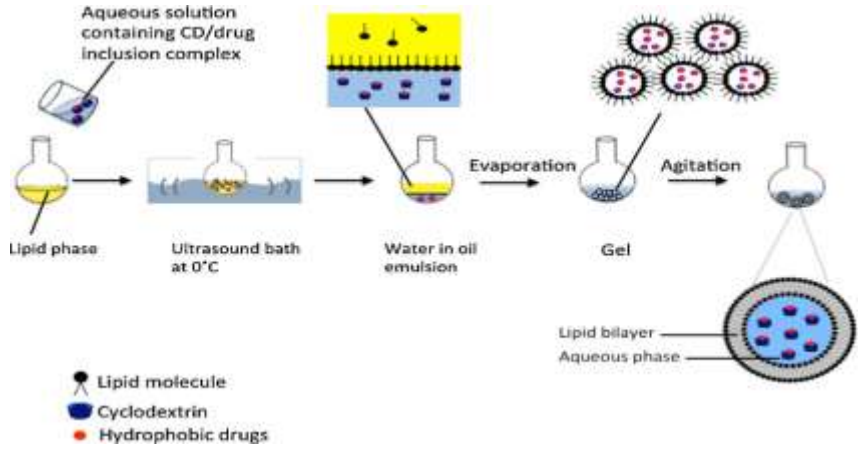


figure.3.5 reverse phase evaporation

When the pressure is lowered, the organic solvents separate and a thick gel is formed. As the remaining solvent separates during prolonged rotatory evaporation at low pressure, the liposomes take shape. This technique can achieve high encapsulation effectiveness of up to 65% in a low ionic strength media, such as 0.01 M NaCl. Small, big, and macromolecules have all been encapsulated using this technique. The primary disadvantage of the method is that the materials to be encapsulated come into contact with organic solvents and short bursts of sonication. Certain proteins may become denaturated or DNA strands may break as a result of these circumstances. The modified reverse phase evaporation process, which has the primary advantage of producing liposomes with a high encapsulation effectiveness of over 80%.

3.1.5. Detergent Removal

Lipids have been solubilized by detergents at their critical micelle concentrations (CMC). The micelles get better at phospholipid as the detergent separates from them, and eventually they unite to form LUVs. Dialysis was used to get rid of the detergents. For the removal of detergents, a commercial device known as LipoPrep is available. It is a dialysis system variant. Equilibrium dialysis is the process of doing the dialysis in dialysis bags submerged in sizable buffers free of detergent. Removal of mixed micelles by detergent (cholate, alkyl glycoside, Triton X-100) (absorption). In order to achieve detergent absorption, a mixed micelle solution is shaken with beaded organic polystyrene adsorbers. Detergent adsorbers have the significant advantage of being able to remove detergents that have a very low CMC and are partially exhausted. Removal of mixed micelles by detergent (cholate, alkyl glycoside, Triton X-100) (absorption). In order to achieve detergent absorption, a mixed micelle solution is shaken with beaded organic polystyrene adsorbers. Other methods have been employed to get rid of detergents: (a) Using Gel Chromatography ;(b) Triton X-100, a detergent, is adsorbed or bound Bio-Beads; (c) Octyl glucoside, a detergent, is bound to Amberlite XAD-2 beads.

3.2. Large Scale Formulation Method

3.2.1. Supercritical Fluid Technology

SCF stands for supercritical fluid, which has characteristics halfway between those of a gas and a liquid. Maintaining the substance at pressure and temperature above critical values will allow for this. Supercritical CO2 (SC-CO2) is the SCF that is most frequently utilized. Being the least expensive SCF, it is distinguished by its low environmental risks and low toxicity. Based on the solids' solubility in SCF, there are essentially two methods for using SCFs. The first method uses a heated spray nozzle to allow a solid solution in an appropriate SCF to pass through. This is for solids that dissolve in SCF. Pressure and temperature below the surface of expansion significantly decrease as it expands into a broader for solids that refuse to dissolve in an appropriate SCF, a solid solution in an appropriate solvent is created using the second method. The prepared solution is then bubbled with SCF. Solid particles precipitate as a result of the SCF's anti-solvent action. We refer to this process as the "supercritical anti-solvent" (SAS) technique. The main benefits of the SCF technique are low residual solvents, gentle operating temperatures, and straightforward operation. However, the approach has significant drawbacks, including costly apparatus and the challenge of using SCF on a wide scale. For solids that refuse to dissolve in an appropriate SCF, a solid solution in an appropriate solvent is created using the second method. The prepared solution is then bubbled with SCF.

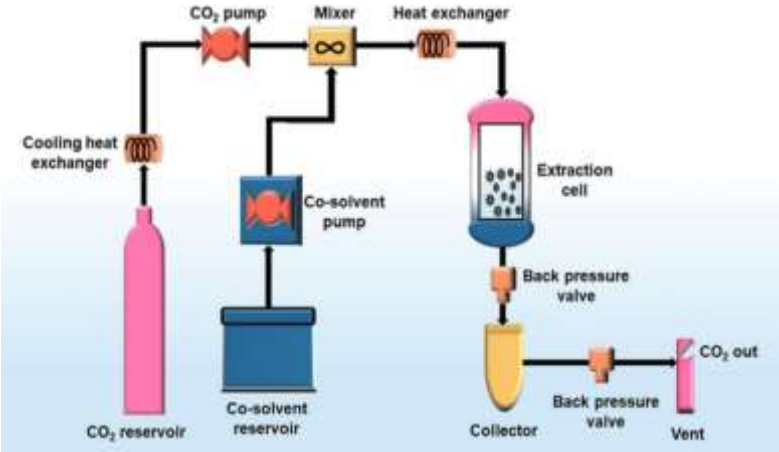


figure.3.6 supercritical fluid

Supercritical fluid technology (SCF) has been applied recently to a number of pharmaceutical industry processes, such as coating, product sterilization, drug delivery preparation, crystallization, and particle size reduction. Additionally, it has shown promise in the formation of particulate drug delivery systems like liposomes and nanoparticles, which improve drug stability and control drug administration. As a result, they may be utilized in the formulation of DPIs. SCF technique has several benefits, such as the ability to process pharmaceuticals in mild circumstances, which is beneficial for labile proteins and peptides, and the ability to produce particles with a restricted size distribution and controlled shape. Additionally, SCF technique guarantees the total elimination of organic solvents. Using SCF technology, our group has created drug LDPF. Drug and lipids were dissolved in acidified methanol and chloroform, which are known to be partially or completely miscible with a SCF antisolvent (usually CO 2). After that, the liquid solution was sprayed into the flowing SCF via a nozzle or capillary. The medication and lipids do not dissolve into the antisolvent after the liquid solvent does. Dry liposomes with a micron size were the outcome. To administer an adequate dosage of drug into the lungs, these liposomes can be combined with carrier lactose.

3.2.2. Lyophilization

According to freeze drying, also known as lyophilization, is used to reduce the rate of lipid breakdown during storage. However, because freeze drying comprises two stressful stages freezing, at which ice crystals might puncture the liposomes, and drying, at which vacuum is applied to sublime the ice it may injure the liposome structures itself. This stressful procedure may cause liposomes to aggregate or fuse, allowing the initially contained substance to seep out. By adding cryoprotectants (such as carbohydrates) before freezing the liposomes, the harmful effects of freeze drying can be reduced. Thus, in order to protect the liposomes against aggregation, fusion, and leakage of the originally entrapped material, cryoprotectants such as lactose, trehalose, sucrose, and other sugars are required during the freeze-drying process (lyophilization). Differential scanning calorimetry (DSC) is

used to detect potential phase transition modifications in liposomes after freeze drying. Before being administered, the freeze-dried substance can be reconstituted by rehydrating to obtain liposomes. But it's crucial to remember that freeze drying is an expensive and time-consuming process. Before and after freeze drying, there were no physical changes observed in the liposome preparations. On the other hand, it shortened the time needed for reconstitution and boosted stability.

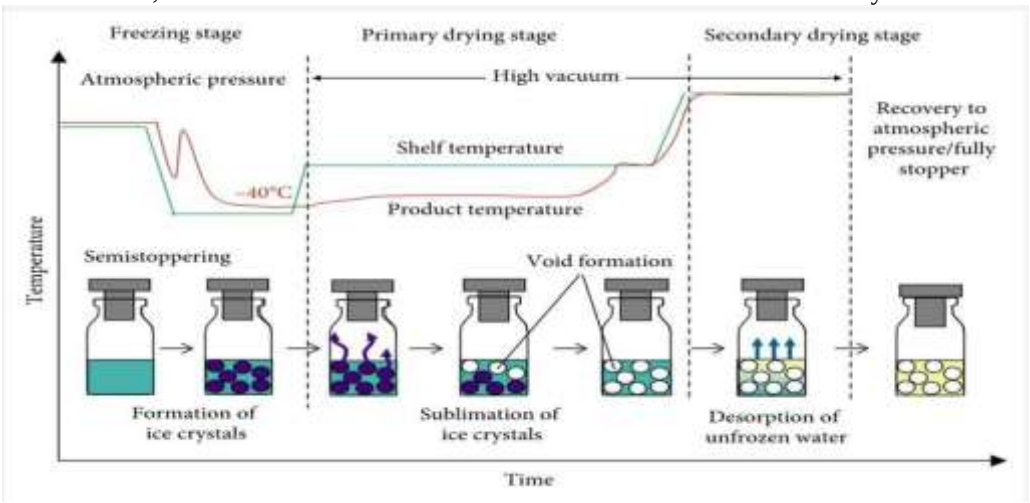


figure.3.7 lyophilization

Another well-liked solvent-based method is SFD, which works best in situations where traditional spray drying isn't appropriate. There are two primary phases of SFD: First, using an appropriate spray nozzle (similar to one used for spray drying), the prepared solution is sprayed into the freezing chamber above the cryogenic medium. Liquified nitrogen (− 196°C) is a traditional cryogenic agent. As the solution exits the spray nozzle, the incredibly low temperature causes the water to quickly solidify into ice. Second: The product that has solidified is transferred to a different chamber where it is sublimated using a vacuum and mild heating. Numerous alterations to the traditional SFD have been created. Spray freezing into liquid (SFL) is one method in which the solution could be sprayed below the cryogenic liquid. Spraying the solution against the flow of chilled gas (-60°C) is an additional adjustment. Spray freezing into gas (SFG) is the term used to describe this procedure. However, generally speaking, the freeze-drying method is an expensive and time-consuming procedure with two major drawbacks that are fixable: The freezing stage is very taxing and there's a good chance that ice crystals will harm dried particles.

Spray Freeze drying entails lyophilizing the medication solution after it has been sprayed into a freezing medium, commonly liquid nitrogen. In contrast to spray drying, this method yields nearly 100% of the product as light, porous particles with improved aerosol performance. Spray freeze-dried liposomal ciprofloxacin powder has been prepared using this approach for inhaled aerosol medication administration. This work uses the spray freeze-dried procedure, which depends on the spontaneous synthesis of liposomes and addresses many of the issues faced by earlier formulations and manufacturing techniques. However, because it involves using more liquid nitrogen and needs longer time for the freeze-drying stage, this is an expensive procedure that would only be justified for expensive pharmaceuticals.

3.2.3. Thin-Film Hydration Method

The most popular and straightforward technique for making MLV was thin-film hydration. Step 1: A mixture of cholesterol and phospholipids is distributed using an organic solvent. The organic solvent was subsequently extracted using a Rotary Evaporator operating at low pressure which combine to generate a uniformly thin lipid film at 45–60 degrees Celsius while it is under suction. Nitrogen gas is utilized to completely remove any residual solvent. Step 2: For one to two hours, the lipid layer is continuously stirred at a temperature above the lipid transition temperature of 60 to 70ºC while being hydrated with an aqueous buffer solution, such as phosphate buffer at pH 7.4. To achieve complete lipid hydration, the liposome suspension is incubated at 4ºC for the entire night. This technique proved to be the most straightforward for producing heterogeneous multilamellar liposome vesicles (MLVs) in terms of size and form. Several methods, including sonication for the generation of SUVs and extrusion through polycarbonate filters for the formation of LUVs, are used to reduce the size of the liposomes. By dissolving the phospholipids in the organic solvents' dichloromethane, chloroform, ethanol, and chloroform-methanol mixture (2:1 v/v; 9:1 v/v; 3:1 v/v), the thin-film hydration approach is the most popular and straightforward way for producing MLV. When the solvent evaporates under vacuum at a temperature of 45–60 ºC, a thin, homogenous lipid film is created. The leftover solvent must be entirely removed using nitrogen gas. In the hydration process, a solution of distilled water phosphate buffer, phosphate saline buffer and normal saline buffers employed. The pH of this solution is 7.4. At a temperature of 60–70 ºC, the hydration process about one to two hours. The liposomal suspension is left overnight at 4 ºC to achieve complete lipid hydration. Any form of lipid mixture can be treated using the thin-film hydration technique. The method's primary shortcomings are associated with low encapsulation, challenging scalability, and a heterogeneous size distribution.

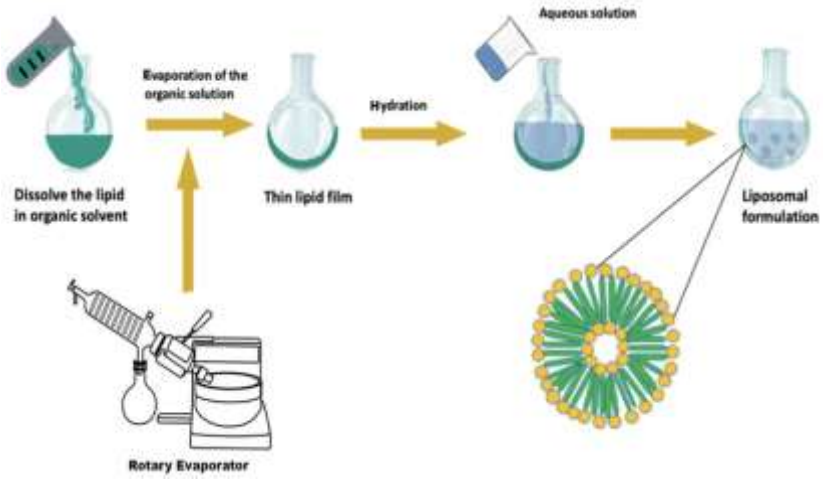


figure.3.8 thin film hydration

3.2.4.Ether /Ethanol Injection Method

- **Ether Injection:** To begin with step in making a lipid arrangement is dissolving the lipids in a natural dissolvable (ethanol). After that, the lipid arrangement is steadily infused either beneath vacuum or at 55–65°C into a fluid buffer containing the medicine to be typified. Beneath vacuum, liposomal vesicles are shaped when natural dissolvable is evacuated. The essential disadvantage of this method is that chemicals to be typified may be uncovered to natural solvents, which may cause heat-sensitive medicines to degrade. At between 55°C and 65°C, or beneath lower weight, an arrangement of lipids broken up in diethyl ether or an ether-methanol blend is dynamically pumped into a watery arrangement of the fabric to be typified. The ether is hence evacuated beneath vacuum, which comes about in the arrangement of liposomes. The technique's essential downsides are the population's heterogeneity (extending from 70 to 200 nm) and the compounds' presentation to natural solvents at tall temperatures.

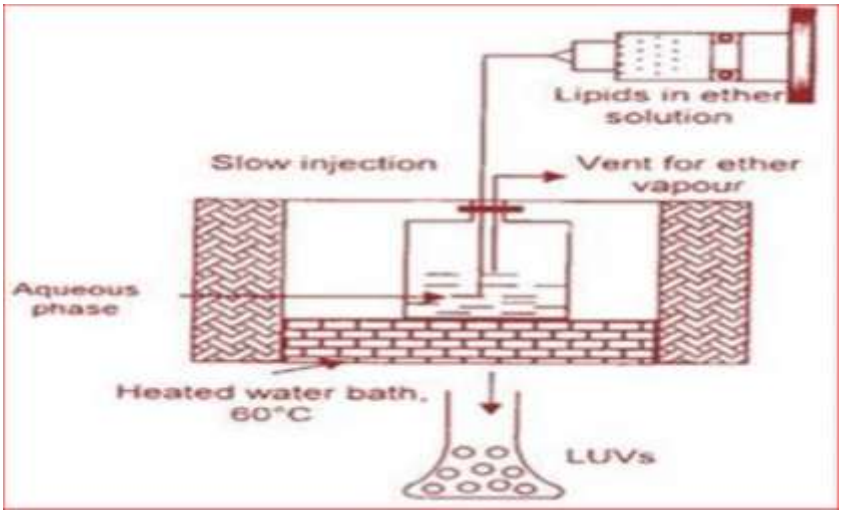


figure.3.9 ether injection

- **Ethanol Injection:** An enormous abundance of buffer is instantly infused with an ethanol lipid arrangement. Promptly, the MLVs are delivered. The method's downsides incorporate a heterogeneous populace with sizes extending from 30 to 110 nm, exceptionally weakened liposomes, challenging ethanol evacuation due to ethanol's inclination to shape azeotropes with water, and a tall probability of naturally dynamic macromolecules inactivating in the nearness of indeed little sums of ethanol.

3.2.5. Micro Fluidization

A process known as micro fluidization, or micro emulsification, is utilized in the large-scale generation of liposomes. The union of antimicrobial liposomes utilizing the thin-layer hydration approach, which was taken after by miniaturized scale fluidization to deliver halfway homogenization and sonication with a bath-type sonicator. Small scale fluidization is a repeatable strategy that produces liposomes with predominant watery stage embodiment. For the reason of making liposomes, a procedure based on miniaturized scale fluidization, smaller scale emulsification, and homogenization was made. A plot plant based on this innovation can item generally 20 gallon/minute of liposomes in 50-200 nm estimate run. It is conceivable to accomplish an embodiment proficiency of up to 75%. Liposomes in fluid scatterings habitually agglomerate or meld and can be subject to oxidation and/or hydrolysis.

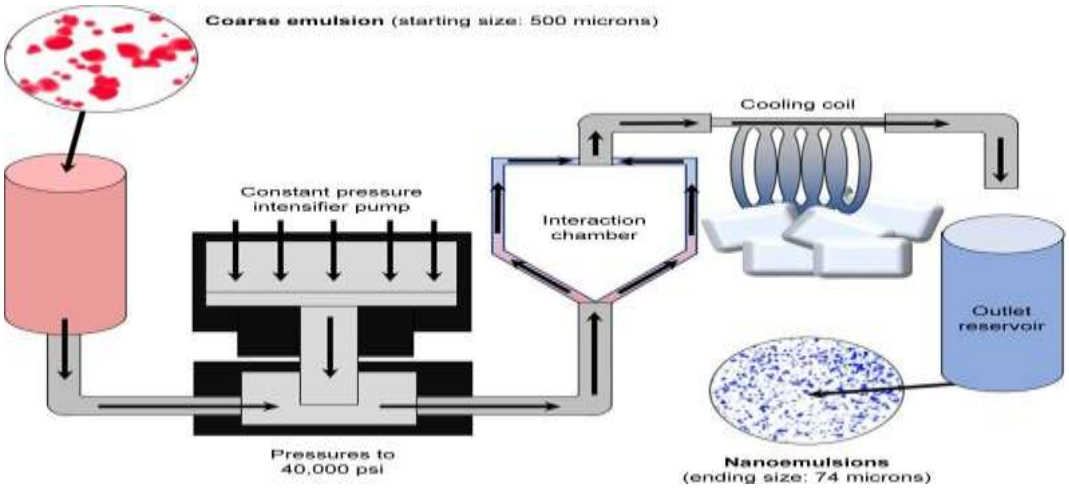


figure.3.10 micro fluidization

4. CHARACTERIZATIONS OF LIPOSOMAL DRY POWDER INHALER

4.1. Flow Behavior

The Angle of Repose is an exceptionally valuable device for deciding the stream properties of a powder; if the point of rest is less than 25 °, the powder will display fabulous stream properties; if it is between 30 and 35 °, the powder will show great stream properties; and if it is more noteworthy than 40 °, the powder will show destitute stream properties. The Point of Spatula is another device that gives a sign of the inner contact between particles; it is the modern Point of rest that the fabric shapes relative to the edge surface; bulk solids with a Point of Spatula less than generally 40 ° are considered formula:

daer (MMADt) = $\sqrt{\rho} \times$ d (VMD)

where, ρ is tapped thickness in units of g/cm 3 and d is volume cruel breadth in µm.

4.2. Moisture Content Determination

The formulation's moisture content may affect inhalation characteristics via influencing stability and flow qualities. The Karl Fischer Titration technique is typically used to determine the moisture content of LDPF.

4.3. Drug Retention and Stability Studies

It is conducted on the LDPFR for long-term stability at 5 °C ± 3 °C for 12 months and accelerated testing at 25 °C ± 2 °C/60% RH ± 5% RH for 6 months. In all storage scenarios, the product is kept apart in its final packaging. Samples from every batch kept under different storage settings are taken out at certain intervals, rehydrated with water for half an hour, and their size, zeta potential, and percentage of medication retained in the liposomes are measured. Additionally, the samples are checked for caking, discoloration, and moisture uptake percentage. The LDPF undergoes comparative drug retention experiments for long-term stability at 5 °C ± 3 °C for 12.

4.4. Surface Topology-

- **By Scanning Electron Microscopy**: To ascertain the size, shape, and surface morphology of the representative LDPF formulations as well as to monitor the liposomes tendency to aggregate with carrier particles, scanning electron microscopy is used. Software for picture analysis is used to evaluate particle characteristics and surface topography. The following describes how characteristics like roundness and aspect ratio can be ascertained. Roundness: This property describes how round an item is, as calculated by dividing its perimeter by its area (4 ' area). Aspect ratio, as defined by Major Axis/Minor Axis, is the ratio between the major and minor axes of the ellipse corresponding to the object (that is, an ellipse with the same area, first and second-degree moments).
- **By NMR Microscopy Method:** With the aid of a polarizing microscope and 31 P-NMR spectroscopic method, the form and lamellarity of liposomes were assessed. To examine the size and form of liposomes, transmission electron microscopy is also frequently employed.

4.5. Ex-vivo lung Tissue Models

Accurately estimating the pulmonary biopharmaceutics of DPI drugs has proven to be difficult, despite the substantial scientific interest in their delivery for both local and systemic impact. There are currently models available for examining lung absorption and disposal of inhaled medicinal compounds, including in vivo, in vitro, and ex vivo models.

Ex vivo tissue models have been used more often than in vitro models in pulmonary biopharmaceutics research when it comes to understanding the mechanisms underlying drug transport and lung disposition kinetics. Isolated perfused lung (IPL) is one of the most helpful techniques. In IPL, the lung is removed from the body and kept in a synthetic environment under specific experimental conditions. This allows confounding whole-body issues, such as distribution, metabolism, and elimination, to be separated from lung-specific evaluations. Compared to reconstructed in vitro monolayer models from a single cell type, an isolated organ experiment like this one must be a closer simulation of the in vivo state because it preserves the architecture and functionality of the tissue. An IPL made from small rodents has been used most frequently for the lung disposition experiments. Recent advancements in kinetic modeling techniques and technology have made it possible to systematically delineate several, intricate lung disposition pathways. Notwithstanding its limitations regarding short viable durations of two to three hours and the

probable absence of tracheobronchial circulation, this ex vivo model (IPL) has been demonstrated to be kinetically predictive of in vivo with respect to macromolecular distribution.

4.6. Percent Drug Entrapment

PDE, which is determined by removing the unentrapped drug from hydrated liposomal suspension, is crucial for both high drug loading and cost control in liposome encapsulation. When it comes to medications that are soluble in water, the free medicine is separated using either a high-speed centrifugation to settle the liposomal pellet or a Sephadex column. Centrifugation at a low speed is used to settle the free drug that is micron-sized for medications that are insoluble in water. Nevertheless, as opposed to low-speed centrifugation, the use of a Sephadex column guarantees total separation. Following the lysing of the liposomes with triton X 100 (0.1% v/v), the medication was examined using an appropriate analytical technique.

4.7. Size & Size Distribution

Particle size analyzers using laser light scattering and the photon correlation concept were used to measure the size and size distribution of liposomes both before and after they were incorporated into LDPF. In LDPF, nanosized liposomes (less than 200 nm) have demonstrated superior performance in preventing macrophage absorption and promoting more even particle dispersion. The mean aerodynamic diameter of the medication or drug carrying carrier particles, once incorporated into LDPF, should not exceed 5 µm for pulmonary deposition. Particle size analyzers using laser light scattering and the photon correlation method were used to measure the size and size distribution of liposomes both before and after they were incorporated into LDPF. In LDPF, nanosized liposomes (less than 200 nm) have demonstrated superior performance in preventing macrophage absorption and promoting more even particle dispersion.

4.8. Zeta Potential

The charge that is present on the colloidal systems and the stability of those systems are both indicated by the zeta potential. Because similarly charged particles would repel one another on the surface, a strong positive or negative surface charge on liposomes suggests higher stability and prevents colloidal liposomal particle aggregation.

4.9. Oxidative Index

Liposomes are tested for stability by measuring their percentage of lipid oxidation over time. Lipids oxidize through a free radical chain in the presence of transition metal impurities and certain oxidizing agents. Unsaturated lipids are more prone to oxidation than saturated phospholipids, and their oxidative index reflects their stability.

5.APPLICATION OF LIPOSOMAL DRY POWDER INHALER

5.1. Anticancer Therapy

A liposomal curcumin dry powder inhaler (LCD) was created for primary lung cancer treatment via inhalation. LCDs are a potential drug with excellent therapeutic efficacy for lung cancer inhalation therapy. Inhalation therapy for primary lung malignant development, employing a liposomal curcumin DPI through a freeze-drying method. Liposomal curcumin dry powder inhalers (LCDs) have an aerodynamic air diameter of 5.81 µm and a fine particle fraction of 46.71%, which is suitable for pulmonary transmission. The take-up of LCDs through A549 cells was higher as well as faster compared to free curcumin. Due to cell death, cytotoxicity levels that were high or low on bronchial BEAS-2B epithelial cells and A549 epithelial cells, respectively, produced a substantial selection index.

5.2. Chronic Lower Respiratory Tract Infection

Since liposomal dry powder inhalers (DPIs) can administer medication locally to the infection site, minimizing systemic adverse effects, they represent an effective treatment for chronic lower respiratory tract infections: medication administration Drugs can be efficiently delivered into cells via liposomes, and cationic liposomes are especially good at getting into bacterial cells. Liposomal DPIs can lower dosage frequency, which can enhance quality of life and lower medical expenses. By focusing on the infection site, liposomal DPIs can lessen the requirement for systemic therapy.

5.3. Macrophage Targeting

Alveolar macrophages (AM) are a crucial component of the first line of defense. Numerous inflammatory byproducts, including tumor necrosis factor (TNF)-a, monocyte chemoattractant protein (MCP)-1, and macrophage inflammatory protein (MIP)-2, are produced when they are activated. After lung transplantation, ischemia-reperfusion (I/R) is an inevitable inflammatory reaction that is thought to be brought on by cells in the donor lung rather than circulating leucocytes from the recipient. Anti-TNF-an antibody pretreatment can stop elevated TNF-a levels after acute inflammation. A TNF-a deficit is thought to provide protection against I/Research was done to demonstrate the benefit of macrophage depletion after transplantation. In a buffer-perfused, isolated mouse lung model. That reducing the number of alveolar macrophages will lessen the expression of cytokines and chemokines as well as the degree of lung injury during I/R. The production of cytokines and chemokines was greatly decreased after treatment with liposome clodronate, which was utilized to induce AM depletion.

5.4. Pulmonary Arterial Hypertension

A disruption in cardiopulmonary arterial blood pressure at the intersection of capillaries and alveoli initiates a series of events that culminate in pulmonary artery hypertension (PAH). Pulmonary hypertension (PH) can be characterized as pre- or post-capillary PH. Post-capillary PH results from pressure elevations in the pulmonary venous and pulmonary capillary systems (pulmonary venous hypertension), whereas precapillary PH is caused by a primary elevation of pressure in the pulmonary precapillary PH (e.g., PAH). The pulmonary artery pressure may rise by more than 25 mmHg. An analog of prostacyclin called

iloprost is used to treat PAH, and it needs to be taken numerous times a day (about 6–9). The potential of liposomes to provide an iloprost formulation with prolonged release and lower the frequency of inhalation.

5.5. Protein and Peptide Delivery

Using the spray freeze drying technique, created a dry powder inhalation of insulin-loaded liposomes. When lipid: sucrose was determined to be 1:1:6, sucrose was proven to be the most effective cryoprotectant. Rats treated with 8 IU/kg of insulin after intratracheal instillation demonstrated a successful hypoglycemic effect with a prolonged low blood glucose level and a relative bioavailability of 38.38%. An aerosol insulin carrier based on agglomerated vesicle technology was created by Karathanasis et al. The carrier was made up of liposomes filled with insulin and connected by chemical bridges that could be broken down by cysteine. Insulin that had been encapsulated was released quickly upon breakdown of liposomal walls caused by contact with cysteine. Research conducted on rats demonstrated a sharp drop in glucose levels with cysteine administration.

5.6. Antioxidant Therapy

Any treatment that prevents or lessens tissue damage caused by oxidants is referred to as antioxidant therapy. The goal of pharmaceutical strategies for modifying oxidative stress-induced lung damage has been to raise pulmonary cells' antioxidant capacity. Studies using antioxidants to lessen lung damage caused by oxidants, however, have yielded inconsistent results. The discrepancies between the studies could, at least in part, be attributed to variations in the antioxidant agents' pharmacokinetic properties. Studies have demonstrated that membrane barriers are insurmountable for enzymes including catalase, superoxide dismutase, and the iron chelator deferoxamine. Low-molecular-size antioxidants, like glutathione and a-tocopherol, are well-known for their ability to effectively scavenge free radicals.

FUTURE PROSPECT

The future of liposomal dry powder inhalers (DPIs) looks promising, with advances focused on better formulation methods and improved inhaler designs to boost drug delivery. This includes using new types of lipids, fine-tuning particle size and shape, and creating more efficient inhaler devices. Liposomal DPIs offer several advantages for treating lung conditions, such as targeted drug delivery, better drug stability, and improved absorption. The liposomes help control how the drug is released and protect it from breaking down, which can lead to more effective treatments with fewer side effects. These developments aim to improve the overall effectiveness and safety of lung therapies.

CONCLUSION

Liposomal dry powder inhalers are a promising way to deliver drugs directly to the lungs. They offer better drug stability, controlled release, and fewer side effects. Among the different methods used to turn liposomes into dry powder, spray drying is the most popular. It's a simple, one-step process that can be easily scaled up and creates particles that are the right size for reaching deep into the lungs. Other methods like freeze-drying, spray freeze-drying, and supercritical fluid extraction can also be useful, depending on what the formulation needs. These techniques help improve particle size, drug loading, and stability. To make sure the treatment works well, it's important to carefully design the formulation, optimize the process, and thoroughly test the final product.

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