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Review Paper

A Review: Proliposomes As Effective and Stable Drug Delivery System

Prajakta Kangutkar*, Samruddhi More, Shital Kambale, Dr. D. R. Jadage

Bachelor of Pharmacy, Womens College of Pharmacy, Peth-Vadgaon, Tal- Hathanangale, Dist- Kolhapur. Maharashtra -416112

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ABSTRACT

A new medication delivery method called proliposomes uses dry, granular materials that, when hydrated, produce liposomal solutions. Enhanced stability, prolonged drug release, and better bioavailability are all provided by them. Size, in vitro drug release, and trapping effectiveness are characteristics of proliposomes, which can be made in a variety of ways. They may find use in pulmonary, topical, and oral administration, especially for medications that are poorly soluble. By offering targeted distribution, proliposomes can increase treatment efficacy and lessen adverse effects. They are a desirable choice for pharmaceutical applications due to their durability and adaptability. All things considered, proliposomes offer a promising strategy for enhancing medication distribution and therapeutic results. They are a useful tool in the creation of reliable and efficient drug delivery systems since they can be made to maximize drug release and targeting.

INTRODUCTION

The innovative delivery technologies, Liposomes remain the most promising, widely adaptable, and extensively studied since their discovery by Bangham et al. in 1965. They are structurally made up from phospholipids, that are nontoxic, Biodegradable, while free of pyrogenic, allergy or antigenic reactions. Using appropriate selection, they may encapsulate materials as minuscule as lithium. ion up to polymers the size of several hundred thousand Daltons' worth of genetic material. [1] Liposomes' characteristics have been thoroughly studied for medication delivery, drug focusing, regulated release, and Enhanced solvability. Nonetheless, liposomes are a system of colloids that is rather unstable, as evidenced by their physical and chemical Unstability. [2] Vesicle fusion and aggregation, which are linked to the variations in the size of the vesicles and the shape, are signs of physical instability. loss of material trapped. Serum proteins, synthetic

***Corresponding Author:** Prajakta Kangutkar
Address: *Bachelor of Pharmacy, Womens College of Pharmacy, Peth-Vadgaon, Tal- Hathanangale, Dist- Kolhapur. Maharashtra -416112*
Email ✉: kangutkarprajakta@gmail.com
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polymers, lipid vesicles (liposomes), erythrocytes, reverse micelles, niosomes, pharmacosomes, immunoglobulins, and microspheres and other substances are among the carriers that deliver the medication to the site of action. [3] A liposome is a type of microvesicle where the lipoidal membrane traps an aqueous volume. Both the lipid bilayer and the aqueous space can trap drug molecules. Nowadays, liposomes are widely employed as drug carriers to increase therapeutic activity, stability, and minimize negative effects. Since liposomal suspensions can have a short shelf life, it would be helpful to have a way to make liposomes fast, on-site, and with minimal manipulation. These requirements are satisfied by the "pro-liposome" technique. [3] In 1986, (PLs) were identified. Proliposomes are free-flowing, dry granular particles that create liposomal dispersion as soon as they are hydrated or come into contact with bodily fluids. Their composition consists of phospholipid and a powder with pores that dissolves in water. One of the most widely used and cost-effective methods for producing commercial liposome products is proliposome. They are a versatile system since they are easily distributed, transferred, measured, and stored in dry powder form. Liposomes can be created in vitro with the use of A suitable fluid for hydration prior to delivery, or within the body under the influence of biological fluids in the body. [4] It is a versatile system since they are easily distributed, transferred, measured, and stored in dry powder form. Liposomes can be created in vitro by employing a favorably hydrating fluid prior to proliposome delivery, or in-vivo by the impact of bodily biological fluids. Some medications' issues with solubility and bioavailability can be resolved by creating pro-liposomal formulations. [5]

Advantages- [1,5]

- Enhanced intestinal and gastric stability of the medication in capsule form.
- Boost the rate at which a medication that is weakly soluble dissolves.
- Boost the permeability Boost intestinal absorption.
- Simple to transform into the appropriate dosage form.
- In contrast to traditional liposomes, can target the medications to non-reticulo endothelial tissues.

Properties of Liposomes and Proliposomes:

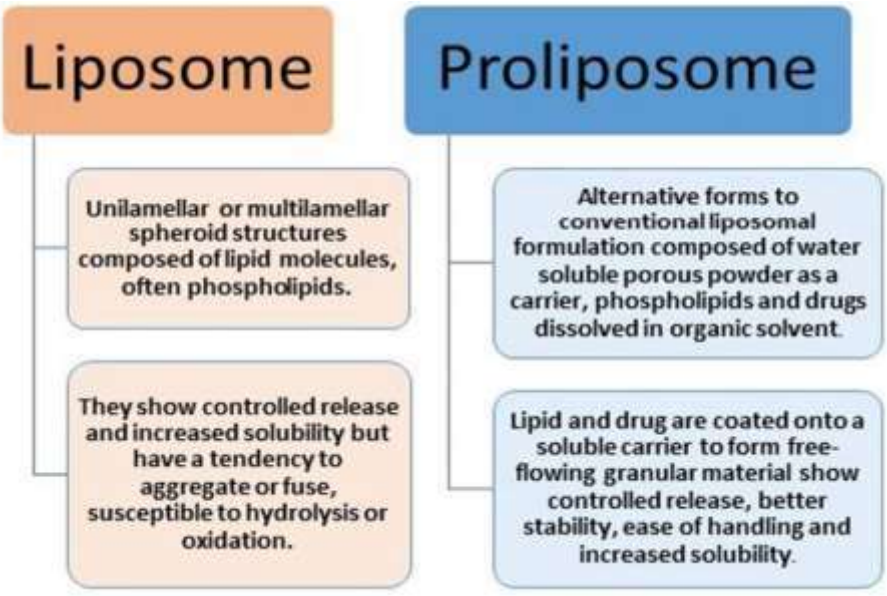

Fig no 1: Properties of Liposomes and Proliposomes

Methods for Preparation of Proliposomes:

There are Some of the commonly used methods in the preparation of Proliposomes such as:

1.Film deposition on carrier method.
2.Spray drying method.
3.Fluidized-bed method.
4.Supercritical anti-solvent method.

1.Film deposition on carrier method:

The technique of thin-film hydration PLs containing CsA which were made using a unique SAS procedure were compared to proliposomes prepared using the standard method, citation. After dissolving n organic solvents, phospholipids, cholesterol, and CsA, the mixture was sonicated (using an Jeio Tech Co., Ltd., Seoul, Republic of Korea; Ultrasonic Cleaner UC-20) until it was transparent and uniform. The medication-lipid mixture was then progressively put into a round-bottomed flask containing anhydrous lactose. After that, the flask was attached to an SB-1200 EYELA water bath and the N-1110V-W rotary evaporator is manufactured by EYELA in Shanghai, China. The temperature was kept at 45°C for Film-EPCS and 60°C for Film-DSPG PLs while combining. To create a coating on the vessel wall, the organic solvent was then eliminated by lowering the temperature and pressure. After that, proliposomes were gathered and kept at 4°C. [6]

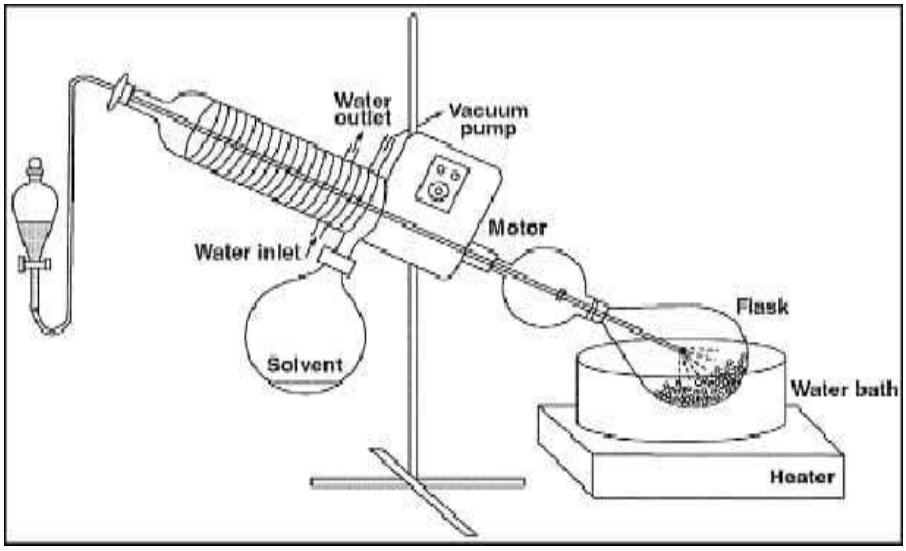

Fig no 2: Preparation of Proliposomes by Film deposition on carrier method

2.Spray drying method:

A spray dryer of the lab kind (Lab-Plant spray model SD-04) was used to create the dried particles. Four steps were engaged in the spraydrying process. Atomization of a material into a spray-air nozzle. interaction, drying of the precipitation in the spray and solids' accumulation item. The drying chamber was first filled with feeding liquid dispersions that included either pure lipids or ethanol containing lipids and mannitol. The displays the The Lipid dispersions' compositions as well as the flow rates that were employed. Using a 1 mm spray nozzle, In the drying chamber, the dispersions were atomized at 90+5 8C, and they were then n a co-current air flow, it was dried. Before being characterized and used further, the particles that were spray-dried were gathered within a reservoir that was connected to a storm and kept within a refrigerator. [9] for crucimine A mesh spray that vibrates using a average size of pores of 7.0 μm was then used to

spray the created solutions through the nano-spray drier. A feeding rate of 25 milliliters per hour was used to introduce the solutions. The movement rate containing nitrogen was 90 L/min. Temperatures at the inlet and outflow were maintained at 90°C and 45°C, in turn. In anticipation of further research, The SD/P that was prepared were removed out of the drying room and stored at room temperature in desiccators. [7,8]

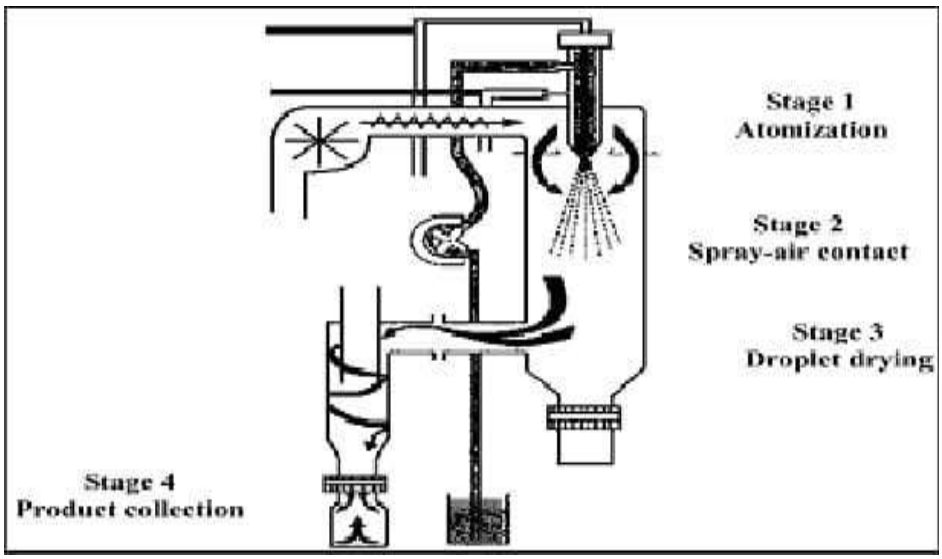

Fig no 3: Preparation of Proliposomes by Spray drying method

3.Fluidized-bed method:

The fluidized bed process is employed for extensive production of PLs. The equipment used to create proliposomes utilizing the fluidized bed approach. Particle coating technology is the basis of this method. In this case, the carrier material can range from non-pareil beads to crystalline powder. When using Non-pareil beads as a material for transportation, the Pareil beads are first covered with a sealant to create a even surface that can aid in the subsequent coating of phospholipids. This also guarantees the formation of a thin, uniform coating of phospholipids surrounding the center and small liposomes when those beads are hydrated. Through a nozzle, The carrier substance is misted with an chemical solvent and medication remedy. At same time, The bed of fluid is vacuumed to take out the organic solvent.After being vacuum-dried for a whole night, the finished lipid-coated powder or beads lose the trace amount of leftover solvent.[9,10]

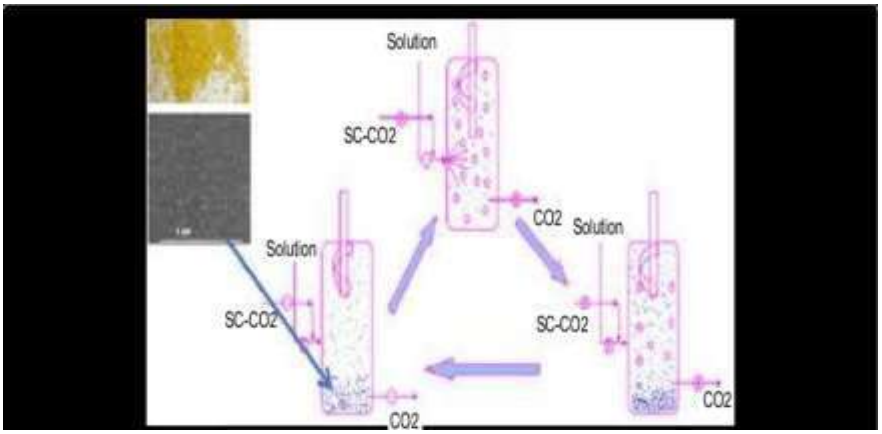

Fig no 4: Preparation of Proliposomes by Fluidized-bed method

4.Supercritical anti-solvent method:

For manufacture of PLs. Due to the three primary forces at play here, Carbon dioxide that is supercritical (ScCO2), which is the fluid condition of carbon dioxide when kept as to a level over its crucial temperature and exertion, is used in the super critical anti-solvent method-

- Reduced solvent residues,
- Easy steps,
- moderate operating temperatures.

We're typically utilize technology that resists solvents to prepare PLs. In those straight forward stages, a device with three components such as a unit for delivering samples, one for precipitation, and one for separation is essentially utilized. The unit that delivers samples is made up of the Two pumps, One is used to transport CO2, which is provided by a 72 cm^3 CO2 cylinder following cooling by a A high-pressure pump with a refrigerator that is employed to Present the CO2 must warm the buffer tank (-7°C); therefore, this reaction vessel's or CO2 cylinder's temperature and pressure should be 45°C and 10 MP. The other pump is regarding the medication solutions, which is introduced via an HPLC pump. Drugs should be dissolved in solvents that are totally miscible with CO2. The phospholipid, cholesterol, and medication are dissolved in organic solvents for both preparations, and then the mixture is sonicated until it is clear and uniform. Nozzle valves We'll open A and B. to allow CO2 to enter those vessels. While Spraying the solution through the nozzle's Through the outer tubule, CO2 is injected into the inner tubule. [11] This apparatus's heat-by-air bath vessel makes up the second half, while A wet gas meter and a separator make up this final element. Due to its low pressure, the separator in the last section separates ScCO2 from the organic solvent; the CO2 is then measured using a wet gas meter. As soon as the temperature and pressure have been brought under control, valve A is opened to let CO2 in, and valve B then permits the medication solution to enter the nozzle. Solution and ScCO2 are combined, along with they quickly diffuse into each other as if in their were sprayed across a coxial nozzle. Once every one of the solutions have been used, these samples are gathered on the filter at the bottom of the tank. after closing valves, A and B and opening valve C to release the vessel's pressure at the initial temperature. To achieve high drug loading PLs, the drug solution's pressure, temperature, and flow rate should all be optimized. [1,12]

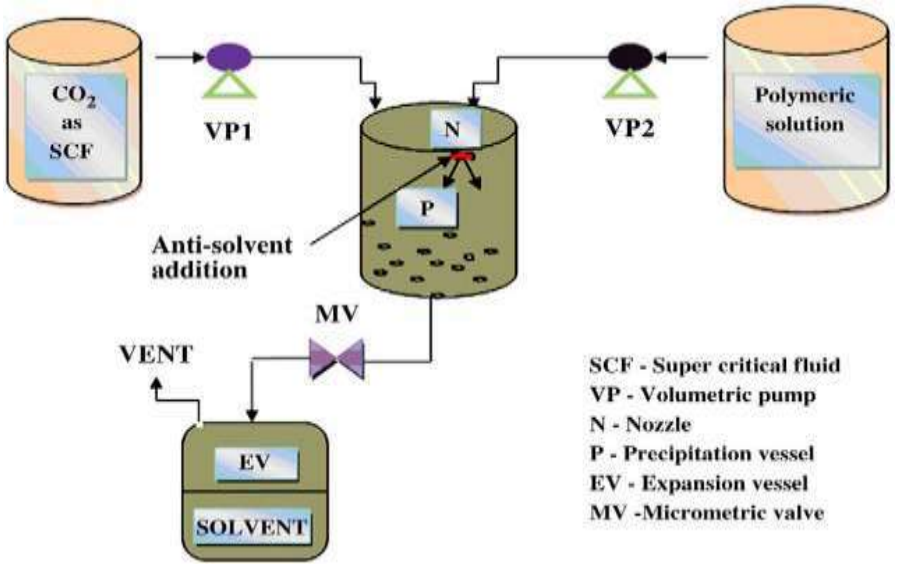

Fig no 5: Preparation of Proliposomes by Supercritical anti-solvent method

Components Used in Preparation of Proliposomes:

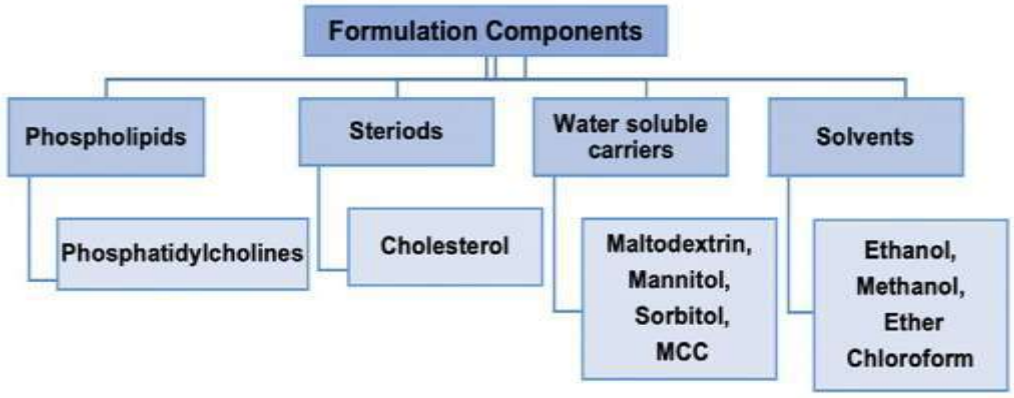

Fig no 6: Components used in Preparation of Proliposomes

1. Phospholipids:

Phospholipids that are most frequently used are phosphatidylcholines (PC). PCs are Another name for lecithin, and they originating from sources, both natural and artificial. Then they vary from more amphipathic compounds in that they form two-layer sheets as opposed to micellar architecture. The most typically used natural sources of PC are egg yolk, soy beans, and, in rare cases, the Spinal cord and heart of cattle. They're commonly utilized as the primary elements in PLs due to their chemical inertness, absence of net charge, and relatively low cost. Sphingomyelin is another component of the neutral lipid bilayers (SM) along with PC. A range of phospholipid structures are produced by combining different chains of fatty acids, such as polar head groups, including phosphatidylglycerol (PG), phosphatidylethanolamine (PE), phosphatidic acid (PA), phosphatidylserine (PS), oleic, lauryl, myristic, palmitic, and stearic acids. The production of PLs are often limited to families of PG and PC despite the wide variety of phospholipids that are available, mostly due to toxicological concerns, purity, steadiness, and cost. [13]

2.Steroids:

A common component of the membrane of the liposome is cholesterol as well as its byproducts. Three known consequences result from their incorporation into liposomal membranes. lowering the membrane's permeability to water-soluble molecules, increasing its fluidity or microviscosity, and stabilizing it when plasma and other bodily fluids are present. It drastically changes phospholipid bilayer properties. when it is incorporated into them. Although cholesterol cannot form bilayers on its own, it can be integrated into phospholipid membranes at large quantities. By increasing the rigidity of the bilayers and reducing their permeability, For hydrophilic drugs, it improves retention; for hydrophobic drugs, it improves encapsulation, but only when the medication is smaller than The ability of the liposome to encapsulate. [14]

3.Water Soluble Carriers:

To help readily alter the amount of carrier required to sustain the chosen carriers and lipids should have a high porosity and surface area. Furthermore, it makes it possible to construct PLs

having a high mass ratio of surfactant to carrier. Additionally, because Since they dissolve in water, they allow the quick Liposomal dispersion formation upon Drinking enough water, along with a somewhat small range Liposomal reconstituted particles can be achieved by regulating the size of the porous powder. Among Sorbitol, magnesium, and microcrystalline cellulose are the carriers that are utilized. Aluminum Silicas, mannitol, maltodextrin, and others. [8,15]

4.Solvents:

They are used to provide vesicles. membranes their flexibility. The most widely utilized solvent mixes or volatile organic solvents include ether, methanol, chloroform, and ethanol. [16]

EVALUATIONS OF PROLIPOSOMES:

1.Scanning Electron Microscopy (SEM):

The PLs specimens were examined via scanning electron Leica microscope microscopy Instruments LEO 440i (Wetzlar, Germany) set to 15 kV accelerating voltage. n a Ringmer, UK-made Pelaron SC7620 sputter coater, Gold was sprayed onto the samples. for 180 seconds With a 0.51 Å s−1 coverage rate with an existing current 3–5 mA, 1 V and 2 × 10−2 Pa of pressure. [17]

2.Transmission Electron Microscopy (TEM):

This technique is also employed to look at the framework of the PL powder followed with liposomes has been hydrated. This procedure involves hydrating this PLs powder and purified water before examining it under a microscope to assess its morphologies and lamellarity. This process keeps going until the lipid layer has been fully hydrated and the carrier has broken down. [18]

3.Hydration Study:

Determining whether a liposomal vesicle forms once the proliposomal formulation is hydrated in vitro is crucial. The fact that liposomes form upon interaction with an aqueous environment is the subject of a hydration research. This technique involves placing a little Dry pro-liposome powder quantity on adding water gently to a glass slide, and then utilizing a microscope to watch for the creation of vesicles. Rapid breakdown and disintegration happen as soon as drinking enough water occurs. Once water comes into interaction with the pro-liposome's lipid surface, liposomes are created. This method is ongoing until this entire Dissolution of the lipid layer and the carrier are hydrated. [19,20]

4.Zeta Potential:

A liposomal solution was produced by putting 10% w/v proliposomal powder in PBS, hydrating it for one minute, and then vigorously stirring it for 30 seconds. The values of the zeta potential, polydispertiy index, and average mean diameter were examined according to the guidelines provided by the manufacturer using Otsuka Electronics Co. Ltd., Osaka, Japan, has an ELS-Z dynamic light scattering (DSL) apparatus. [21]

5.In-vitro Diffusion Studies:

A treated cellophane membrane with 100 mg of proliposome granules placed on one end of an open tube was used to measure the drug's release. The dialysis tube was suspended in 40 milliliters of PBS (pH 7.4) in a 100 milliliter beaker. With a magnetic stirring device, the mixture was agitated as to ambient temperature at 200 rpm. The drug release test was conducted under ideal sink circumstances. At appropriate intervals (at 1, 2, 3, 4, 5, 6, and 24 hours), the samples were taken out. To keep the volume at 40 ml throughout the experiment, the dissolution medium was swapped out for the same amount of brand-new pH 7.4 PBS

solution. After increasing this volume to 5 ml with PBS (pH 7.4), the amount of medication in the extracted samples (1 milliliter) was assessed as to 273.5 nm. These cumulative percentage of medication discharged was then computed and made a time-plot. [17] Predicting medication absorption in vivo may be aided by the in vitro release studies. [22]

6.Flow Property:

Using an angle of repose, the PL powder's flow characteristics were assessed. The angle of repose was ascertained by using the fix funnel method. Ten centimeters above the paper's surface, the PL powder was let fall onto it via a funnel. The angle of repose formula is as follows: [23]

Tan y ¼ 2H=D

APPLICATION:

1.Oral Delivery:

Pro-liposomes aid in improving the dissolving efficiency of medications that are not very soluble. As a result of the greater volume of hydrophobic material inside the liposomal lamellae, its creates multi-lamellar vesicles upon contact with fluid, ensuring greater trapping of insoluble medicines. Additionally, it allows the medication to change from a crystalline to an amorphous state. [19]

2.Pulmonary Delivery:

Additionally, liposomal formulations are designed to provide targeted medication action within the respiratory system. Because Phospholipids, another kind of component of surfactant in the lungs, make up liposomes, medication trapping inside them improves absorption. Liposome-encapsulated medications remain in the bloodstream for a long time and have fewer side effects. [18]

3.Mucosal Delivery:

In vivo, PLs create vesicular structures called liposomes in response to the watery milieu present on mucosal surfaces. They contain phospholipids, which naturally bind to cellular membranes. Additionally, they are often non-irritating and non-toxic2. Improved pharmacological action is provided by the drug's molecular dispersion in the bilayers. [2] Furthermore, because PLs transform into vesicular formations in living things, or inside the mucosa, the challenges related to liposomal preparations, like stability and loading, are avoided. The ability to retain drugs is increased when liposomes, which are created when the mucosal fluid is hydrated, are positioned as drug storage on the mucosa. These medication partitions into the mucosa more readily as a result of the liposomes' noticeably increased mucosal retention. [24]

4.Diabetes:

Numerous studies have examined the viability of employing liposomes as a possible oral delivery mechanism for insulin. When liposome-encapsulated insulin was administered orally to diabetic rats, a change in blood glucose levels was seen. After giving insulin encapsulated in PC: CH liposomes orally to normal rats, Dobre et al. showed a decrease in blood glucose levels1. Intravenous administration PLs work well for administering liposomes parenterally. The primary benefit of PLs is that sterilization is possible without compromising their inherent qualities. [25]

5. Parenteral Delivery:

Sterilization is crucial for parenteral administration. Common methods of sterilization include filtration sterilization, aseptic production, steam sterilization, and γ-irradiation. Because terminal sterilization needs steam at 121°C, it is

inappropriate for liposomal compositions. Lipid hydrolysis at high temperatures destroys liposome structure and increases unsaturated lipid peroxidation**.** For parenteral liposome administration, pro-liposomes are sufficient. [26] Pro-liposomes have the advantage of allowing sterilizing without compromising their inherent properties. Pro-liposomes can be hydrated before to delivery to create a multi-lamellar liposomal suspension, and they can be kept in dry form after sterilization. Pro-liposomes have been active in the field of injectable medication delivery systems throughout the last few decades. The medication's attraction to multi-vesicular liposomes results in a unique sustained-release drug delivery method. Drugs that are liposomally trapped experience a prolonged release over a few days to several weeks. [27]

CONCLUSION:

In future, pro-liposomes may be used as medication delivery vehicles. They provide non-invasive drug delivery through the skin and have made great progress in addressing issues with liposome the solubility, stability, and bioavailability of poorly soluble medications. also Compared to liposomes, proliposomes have a longer shelf life. A preferable option for preparation would be proliposomes. Making use of methods like spray drying and fluidized bed drying proliposomes may be produced and applied topically, parenterally, orally, and they are increasingly in demand in the cosmetics sector. Proliposomes have demonstrated their superior position in contemporary drug delivery systems based on all of these parameters.

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