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Present Prospective of Pro–Liposomes

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Abstract: A lipid bilayer membrane encloses an aqueous compartment in a liposome, a biologically inert microscopic vesicle. The most effective and widely used drug delivery system is liposomes. However, liposomes have a poor stability issue that makes storage a challenge. Pro-liposomes were discovered by Payne et al. in 1986 to solve the stability issue. Pro-liposomes are described as dry, free-flowing particles with a dispersed system that, upon coming into contact with water, instantly form a liposomal suspension. Pro-liposome is helped to improve the bioavailability. This paper reviews the method of preparation, merits, evaluation of Pro-liposomes and highlights its potential to be exploited for different routes of administration and also, we discuss the future aspects.

Keywords: Pro-liposomes, Liposomes, Carriers, Phospholipids and multi-lamellar.

INTRODUCTION

Since the discovery of liposomes in 1965 by Bangham et.al, they continue to be the most promising, broadly applicable, and highly researched of all the novel delivery systems. Structurally they are composed of phospholipids which are biodegradable, nontoxic and devoid of any antigenic, pyrogenic or allergic reactions, and with careful selection, allow encapsulation of matter that is as small as the lithium ion up to macromolecules as large as genetic material of several 100000 Daltons. [1] These properties of liposomes have been broadly investigated for drug delivery, drugs targeting, controlled release and increased solubility. However, liposomes are relatively unstable colloidal system showed by physical and chemical instability. Physical instability is exhibited by vesicle aggregation and fusion, which is associated with changes in vesicle size and loss of entrapped material. [2] Chemical stability is the more importance as it is associated with phospholipids which form the backbone of the bilayer formation. It is of two types namely the hydrolysis of ester bonds linking the fatty acids to the glycerol backbone and other one is peroxidation of unsaturated acyl chains (if present) which accelerates liposome breakdown and alters drug

release characteristics. These factors influence the in vivo performance and storage behavior of the liposomes. [3]

For liposomes to enter the market, they must be stable during the storage period, and remain stable or impaired before reaching their targeted tissues to produce action. Number of approaches have been used to overcome these problems, some of which include, control of particle size and lamellarity, altering the lipid composition, lyophilization, electro steric stabilization etc. From that approaches the one approach which helped overcome the stability issue associated with liposome and led to the development of a new drug delivery system is the Pro-liposome (PL). Discovered by Payne et.al in 1986, Pro-liposomes (PLs) are dry, free-flowing granular products composed of drug(s) and phospholipid(s) which, upon addition of water, disperse to form a multi-lamellar liposomal suspension.[4] It is one of the most cost effective and widely used methods for producing commercial liposomal products. It is based on the intrinsic property of hydrated membrane lipids to form vesicles when contact with water. Existing available in dry powder form, they are easy to distribute, transfer, measure and store making it a versatile system. Liposomes are formed in vivo under the influence of physiological fluids as well as in vitro prior to administration using a suitable hydrating fluid. The liposomes formed on reconstitution are similar to conventional liposomes and more in uniform size. The present review gives a brief overview of preparation, evaluation and application of PL as novel carrier systems.[5]

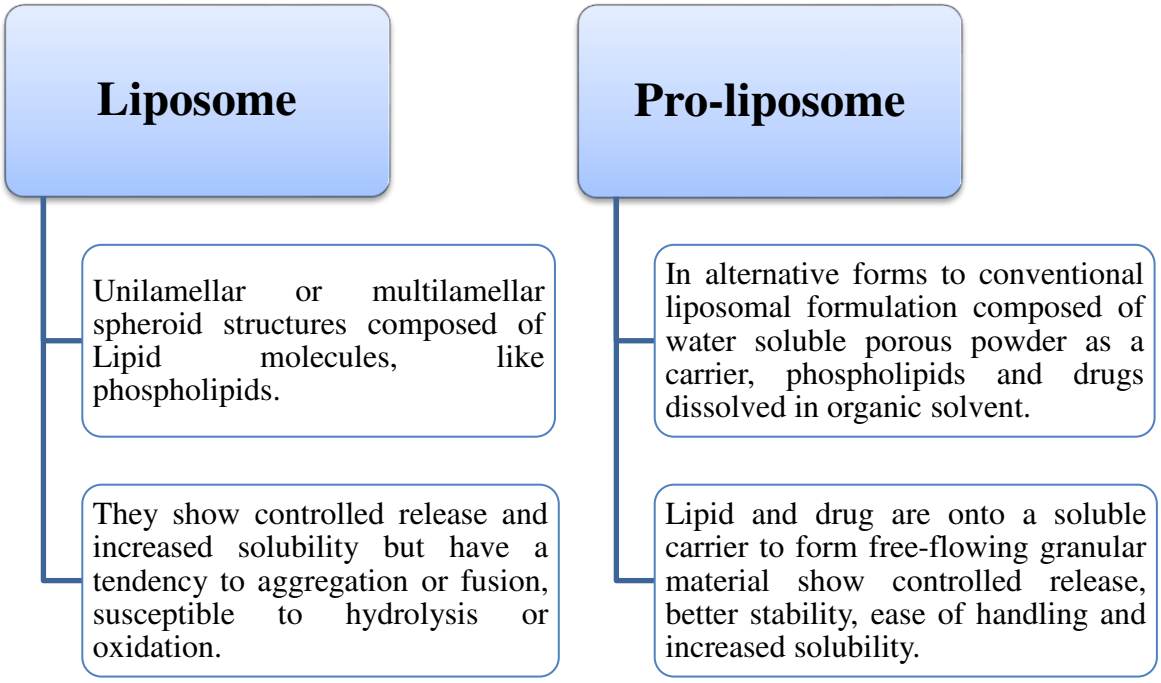

Table. 1- Difference between Liposome and Pro-liposomes

Advantages of pro-liposomes[6,7]

- Increase the dissolution of a poorly soluble drug
- Increase lipophilicity
- Improve the permeability Improve intestinal uptake
- Decrease hepatic first-pass metabolism
- Improve gastric/intestinal stability of the encapsulated drug
- Easy of making into a desired dosage form

Components of pro-liposomes

1. Phospholipids:

The bulk components of the liposomal lipid membrane are phosphatidyl (phospholipid) glycerides, amphipathic molecules that consist of a hydrophilic phosphate head group and hydrophilic fatty acid chains bridged together by a glycerol back bone. In the initial studies, egg phosphatidylcholine (egg CP, egg lecithin) and these phospholipids were used.Although having a single head group composition, contain various lipid species due to the presence of mixed acyl chains and varying lengths. More recently, highly purified lipids have been chemically synthesized from saturated fats with the same carbon numbers. The chain of fatty acids can rangefrom 8-24 carbons (C8-C24); among them,mostoften used in the administration of liposomal drugs are myristic (C14), palmitic (C16) and Stearic (C18). Aside from the carbon length of fatty acids, the phosphatidylcholine (PC) group may vary. Phosphatidylethanolamine (PE), which are zwitter ion (balanced load with positive load on the headset and negative charge on phosphate group), the negatively charged phosphatidyl, serine, and glycerol inositol head group. Many of the physicochemical properties of liposomes such as stability, permeability, phase behaviour and membrane order depend on the fatty acid chain length and saturation.[8,9]

2. Cholesterol:

It is added to enhance the stability of the phospholipid molecule. Cholesterol incorporation in thephospholipid membrane increases the separation between the choline head group and eliminates normal electrostatic hydrogen bonding interaction.[10]

3. Solvent:

Organic solvents are used in the preparation of pro-liposome generally a mixture of chloroform and alcohol (methanol, ethanol). Alcohol is added to stabilise chloroform and prevent the production of gaseous phosphogen. They are also used to for providing the softness for vesicle membrane.[7]

4. Water soluble carriers:

The carrier's chosen should have high surface area and porosity so that the quantity of carrier required can be easily adjusted to support the lipids. It also enables a high ratio of surfactant carrier mass when preparing pro-liposomes. Moreover, being water-soluble, they allow rapid formation of liposomal dispersion on hydration and controlling the size of the porous powder, relatively narrow range of reconstituted liposomes can be obtained. Some of the carriers are utilized include maltodextrin, sorbitol, microcrystalline cellulose, magnesium aluminium Silicates, Mannitol etc.[11]

Method of Preparations

Pro-liposomes (PLs) are prepared by many methods 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 Film deposition on carrier method is used for the composition of Pro-liposomes. In this procedure, the coat of drug and phospholipids is discharged on a pervious, water soluble carrier substance. By viewing Figure 2, an evaporative solution containing a solution of drug and under vacuum the phospholipids is injected drop by drop by a feed tube onto a core of carrier substance which is carried during a vessel of a rotary flash evaporator . At any stated moment, over-wetting of the matrix's is circumvented and following

aliquot of organic mixture is feeding solely when a free-flowing powder matrix is procured. The Selected carriers should exhibit great surface area and permeability in order to regulate the quantity of carrier which is needed to assist the lipids. This surfactant also great permits to carrier mass proportion for the pro-liposomes production. If they are water soluble, they enable fast production of liposomal dispersion on hydration and by properly managing pervious powder size, comparatively limited variety of reconstituted liposomes can be acquired. Mostly used carriers are sorbitol, magnesiumaluminium silicates, microcrystalline cellulose, maltodextrin, mannitol, etc. Stride of solvent inclusion and evaporation which is inactive. To circumvent this issue, alter procedure by dispersing the carrier substance in organic mixture of drug and phospholipids in vessel of rotary evaporator and directing it to vacuum evaporation. By doing so, highly consistent and well-organized lipid distribution is achieved and a stable and less time taking procedure is gained in contrast to the actual procedure.[12]

2. Spray drying method: -

The distinctive attribute of this process is that it reclined in its propensity to include particle composition and drying together in a consistent stride, allowing for more desirable production of particles. 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 can be easily scaled up. Its cost is reasonable and effective for preparing PLs in large quantities. As shown in Figure 3, this spray drying procedure consists of four phases: atomization of the product into a spray nozzle, spray-air association, drying of the spray droplets and collection of the solid product. Liquid dispersions containing pure lipids or lipids and carriers in an organic mixture are first prepared, and then they are poured into the dry cell. Dispersions are atomized into drying cells using a spray nozzle and desiccated in a simultaneous air flow that is then collected in a tank. High temperatures, shearing stresses, and absorption episodes are the main factors affecting this method because they can cause active molecules to degrade mechanically and thermally. It can be improved by enhancing the operational variables. Temperatures of the drying air and the rate of liquid spraying are two examples of working variables. Stabilizing adjuvants like disaccharides, cyclic oligosaccharides, and polyols can be used to protect the unification of active molecules, and by increasing the surface area of lipids, the effectiveness of hydration can be intensified.[13,14]

3. Supercritical anti-solvent method

In that Super critical anti-solvent method for the production of PLs we use Supercritical Carbon dioxide (SCCO2) which is actually carbon dioxide's fluid state when it held at on some level above its critical temp and pressure.

For the preparation of PLs, we use anti-solvent technology. An apparatus consisting of three parts (e.g. a sample delivery is unit, a precipitation unit and a separation unit) it is basically used in those simple steps. Two pumps, one for the delivery of CO2 which is supplied through CO2 cylinder (72 cm) after being cooled down by refrigerator and a high-pressure pump is used introduce it to the buffer tank (-7°C) for preheating thus the conditions of temperature and pressure of thereaction vessel or CO2 cylinder should be 45°C and 10 MPa and the sample delivery unit is made up of one drug solution that is added via an HPLC pump. For the purpose of dissolving the drugs, a solvent that is completely miscible with CO2 should be used. Phospholipids, cholesterol, and drug were dissolved in organic solvents for both preparations, and then the mixture was sonicated until it was uniformly clear. The nozzle valves A and B will be opened to allow CO2 to enter the vessel. The inner tubule of the nozzle is used to spray the solution, while the outer tubule is used to spray CO2. The heated by air bath vessel makes up the apparatus' second component, and a separator and a wet gas metre make up its final component. Due to its low pressure, SCCO2 is separated from the organic solvent in the last part's separator, and the CO2 is measured using a wet gas metre. After reaching the present value of temp and pressure, valve A is open for the entrance of CO2 right after that, valve B allow drug solution to enter the nozzle. Rapidly, the solution and SCCO2 are combined and diffused into one another as though through a coaxial nozzle. Thus, the solute will dissolve in organic

solvent to reach super saturation in a very short period of time about 30 minutes and this all because of the solute'ssolubility in the organic solvent decreases gently, thus the PLs are precipitated in the vessel. After the completely utilization of solution, A and B valves are closed and valve C is opened to depressurize the vessel at the opening temp and in the end,we gather these samples from the vessel's bottom using the filter. To obtain the high drug loading PLs, the pressure, temperature, and flow rate of the drug solution need to be optimised.[15,16]

4. Fluidized bed method

On the large scale production of PLs whose principle relays on particle coating technology, in which carrier material can vary from crystalline powder to non pareil beads. While using non pareil beads as carrier material, first for getting smooth surface pareil beads are coated with seal coating which can help further in coating of phospholipids and which also ensure thin uniform coating formation of phospholipids 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 vacuum. When dried overnight under vacuum, the lipid-coated powder or beads remove the trace amount of remaining solvent.[17]

EVALUATION

1. Solubility Studies

The excess quantity pristine drug and pro-liposome formulations were allowed to be dissolved in pH 7.4 phosphates buffer at 25 ± 0.5°C in the 10 vials which were rotated at 100 rpm in the orbital shaker for 24 hours. Using a 0.8-m membrane filter, the final solution has been purified. The UV-Visible Spectrophotometer was used to determine the concentration of the drug present in the samples.[18]

2. Fourier Transformed Infrared

To verify potential interactions among drug and excipients was performed by Fourier transformed infrared (FT-IR) analysis. The blend of drug and polymers or formulation was dispersed in potassium bromide powder and a KBr press was used to made pellets. From FT-IR spectrophotometer, Powder diffuse reflection on the FT-IR spectrum was taken.[19]

3. Differential Scanning Colorimetry

Differential Scanning Colorimetry performed using the DSC-60 instrument in pure pharmaceutical products and formulations. Alpha-alumina discs of high purity were used as the standard for the empty cell. The complex scans were conducted in the nitrogen atmosphere at 10°C min−1 heat rate. Energy has been estimated as J/Kcal.[20]

4. Particle Size, Zeta Potential Analysis and Polydispersity Index

Malvern Zetasizer (Zetasizer Ver. 6.34, Malvern Instruments Ltd. UK, Sl Number: MAL1045544) was used to determine the charge on the surface, average particle sizes, and their distribution using dynamic light scattering. The experiment was conducted through a transparent zeta cell; water was used as a dispersant with a refractive index (RI) of − 1330 and viscosity (cP) of − 0.88 and a constant temperature of 25°C. The sample has been evaluated three times to reduce error. A polydispersion index, which dimensional number varying from 0 to 1 for monodispersed particles is used to determine the distribution of particles of nanoparticles. Higher value implict a size distribution of less homogenous for nanoparticles.[21]

5. X-ray Diffraction

X-ray diffractometer was utilised to analyse the crystalline nature of the samples. It has been done using XRD on a Cu target with Kb-filtered radiation. We have scanned both theta scales from 5 to 40 degrees. The X-ray diffraction unit cell parameters (a, b, c, and α, β) data, and 5°/min scanning speed for the recording with steps of 0.02° were provided by Biocon Limited, Bangalore, India.[3]

6. Scanning Electron Microscopy and Hydration Studies

A scanning electron microscope was used to determine the surface morphology of the formulations. The formulation samples were mounted on an adhesive double-sided aluminium framework, which was screened before observation at a 25 kV accelerated voltage, and sputtered under vacuum with gold. Data were gathered from the SURA laboratory in Hyderabad, India. The optical microscopic method was used to carry out and confirm the hydration

process of pro-liposomes. A glass slide was covered with the pro-liposomes, and some water was added. For the formation of liposomes, pro-liposomes were seen. Before adding water, free-flowing pro-liposomes were also seen under a microscope. Under a 100x magnification, they were observed.[22]

7. Drug Content

A total of 1000 mg of sample formulation was taken in a 50-mL volumetric flask containing methanol (100%) as a solvent of extraction and allowed to dissolve for drug extraction from pro-liposomes (1st dilution). Aliquots 5 mL of previous solution were further diluted with methanol (100%) in 25-mL volumetric flask. Then, using a UV-Vis spectrophotometer (Shimadzu- UV 1800, Japan), absorbance at 237.7 nm was used to determine the drug concentration.[16]

Percentage Yield (% Yield)

The process of weighing the initial excipients used to prepare the pro-liposomes and the pro-liposomes themselves, i.e. product weight, phospholipid, carrier and cholesterol used in the preparedness, were used for the percentage yield of pro-liposomes. The formula was used to determine the percentage rates. [22]

$$\text{Percentage yield} = \frac{\text{Mass of proliposomes}}{\text{Mass of drug þ Mass of the excipients}} \times 100$$

8. Percentage Encapsulation Efficiency

The prepared pro-liposomes were put on the centrifuge tube and spun at 15,000 rpm for 30 minutes. The centrifugation technique was used to calculate the pro-liposomes loaded with SV's percentage effectiveness. The prepared pro-liposomes were placed in a centrifuge tube and spun at 15,000 rpm for 30 minutes. One millilitre of the supernatant has been taken out and diluted with methanol. The samples were appropriately diluted prior to measuring UV absorption. The unentrapped SV was measured using a UV-spectrophotometer at 237.7 nm. The entire drug, free from the formulation, is provided by the free SV in the supernatant. A percentage of the drug trapped in the capsules indicates how effective the process was. [23]

$$\%\text{Encapsulation efficiency} = \frac{\text{Total mass of the drug} - \text{free dissolved drug}}{\text{Total mass of the drug}} \times 100$$

9. In Vitro Diffusion Studies

In 900 mL of phosphate buffer pH 7.4 (dissolution media) in a paddle type (USP II dissolution apparatus), 100 mg of accurately weighed drug, physical mixtures and pro-liposome formulations were added. The mixtures were then stirred at 50 rpm at 37 0.5°C. At 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11 and 12 hours, five-milliliter aliquots were removed and replaced with five millilitres of fresh media. The collected samples were analysed for drug content with appropriate dilution at 237.7 nm using UV-visible spectrophotometer against the blank.[24]

APPLICATIONS

Oral delivery

Oral drug delivery continues to be the preferred route of administration, but liposomes have limited success in delivering drugs through the oral route. This is due to the absence of a stable dosage form oral delivery and erratic and unpredictable absorption profiles shown by liposomes. Being available as a free-flowing powder, PL represents the first example of delivering liposomes into a solid dosage form such as tablets or capsules. Further, liposomes are created at the site of absorption when they come into contact with biological fluids, preserving their integrity. Zaleplon is a hypnotic medication used to treat insomnia and has anticonvulsant potential. Due to its limited aqueous solubility and extensive first-pass metabolism, it shows poor bioavailability of 30%. PLs for oral delivery of Zaleplon and found 2-5 fold improvement in oral bioavailability in rats compared to pure drug.[9,25]

Arthritis

The drug that is being in arthritis especially steroids is destroyed by their side effect. On local administration into the joints, the drug diffuses easily from the site of injection and its action on the

inflamed area is only transient. Segal et.al suggested that liposomes could be used in the treatment of local diseases. It is observed that steroids (e.g. cortisol palmitate) can be entrapped into large multilamellar liposomes composed of dipalmitoyl phosphatidylcholine and phosphatidic acid. These preparations, when ingested into rabbits with experimental arthritis, can decrease the temperature as well as the size of the joints to a greater extent than with a similar amount of free steroids.[26]

Diabetes

The feasibility of using liposomes as a potential delivery system of the oral delivery of insulin has been extensively studied. Alteration in blood glucose level in diabetic animals was obtained by the oral administration of liposome encapsulated insulin. Dobre et.al demonstrated a lowering of blood glucose level in normal rats following the oral administration of insulin entrapped in PC: CH liposomes1. Parenteral delivery PLs are well suited for parenteral application of liposomes. The main advantage associated with PLs is that it allows sterilization without affecting the intrinsic characteristics. Besides, they can be stored as sterilized in the dry state and can be hydrated prior to administration to form multilamellar liposomal suspension.[27]

Pulmonary delivery

Additionally, liposomal preparations are designed for targeted drug action in the respiratory system. As phospholipids, which are also found in lung surfactant, make up liposomes, drug entrapment within them leads to improved absorption. Drugs contained in Liposomes are present in the blood for a longer time and with fewer side effects. The following three apparatuses are used for pulmonary drug delivery.[28]

i) Pressurized metered dose inhalers (pMDI):

The liquefied propellants are mixed with a drug solution or suspension. Chlorofluorocarbons are replaced by hydrofluoroalkanes because they do not destroy the ozone layer and are less soluble in phospholipids. These propellants allow for the suspension of pro-liposomes, which serve as a liposome carrier for the pulmonary route.

ii) Dry powder inhalers (DPIs):

It involves the inhalation of drug as fine powder that causes dispersion of drug directly into airstream of patient. Dry powder inhalers have many advantages, including controlled delivery, reduced toxicity and increased potency, even local drug displacement, increased patient compliance, improved stability, and significant drug entrapment. Since pro-liposome formulations come in dry powder form, they are best used for dry powder inhaler delivery of liposomes. Dapsone dry powder inhaler with spray dried liposomes entrapped has prolonged drug action in lungs to prevent Pneumocystis carinii pneumonia. 16 hours of prolonged drug release are predicted by in vitro studies.

iii) Nebulizers:

Although it is the simplest way to deliver liposomes to the respiratory system, drug instability and liposome leakage can cause problems. In order to solve this issue, dry powder formulations are used. Pro-liposomes are therefore effective nebulizers of liposomes.

Mucosal delivery

Pro-liposomes 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. Increased therapeutic action is brought on by the molecular dispersion of the drug into the bilayer. The vaginal pro-liposomal formulation of Clotrimazole has prolonged release of drug and may enhance the drug retention time within the mucosa that leads to better antifungal effect.[29]

Transdermal delivery

Pro-liposomes are made up of phospholipids that naturally bind to skin lipids, increasing the drug's ability to permeate the skin. Pro-liposomes are transformed into liposomes upon hydration, resulting in the entrapped drug's continued action. The development of liposomes in an aqueous environment controls skin diffusion. In order to increase skin permeation, one should avoid the stratum corneum's obstruction. Pro-

liposomal formulations of nicotine and aceclofenac have been developed for long-lasting transdermal action.[30]

Ocular drug delivery

Due to precorneal loss effects, conventional ocular medications have poor bioavailability. 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. It is simple to use liposomal formulations for ocular drug delivery. Ciprofloxacin liposomal hydrogels are used to protect catheters from bacteria.[24]

CONCLUSION

Pro-liposomes are potential drug delivery systems in the future. They offer non-invasive drug delivery across the skin and have made significant strides in resolving the stability, bioavailability, and solubility of poorly soluble drug problems associated with liposomes. Due to their greater physical and chemical stability and potential for scalability for commercial viability, they are a better alternative to the liposomal vesicular system. They can be prepared into unit dosage forms, such as tablets, capsules, and beads, etc., because they are in dry powder form. Pro-liposomes have been used for a wide range of pharmaceutical applications because of all these benefits. Pro-liposomes are administered orally, parenterally, topically as well as used in cosmetic and hair technologies, sustained release formulations, diagnostic purpose and work as good carriers in gene delivery. Pro-liposomes are becoming a useful drug carrier for different delivery systems. Pro-liposomes are still being used to develop new delivery systems for nutraceuticals, herbal actives, and other synthetic formulations. In order to create scale-up batches for pharmaceutical and natural preparations, more research should be conducted.

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