

## Proliposomes: An Approach for the Development of Stable Liposome

### Proliposomas: Una aproximación para el desarrollo de liposoma estables

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#### RESUMEN

**Antecedentes:** durante varios años, se han realizado muchos intentos para mejorar la estabilidad liposomal. En 1986, Payne et al, introdujeron el concepto de pro-liposoma para la preparación de liposoma con el fin de evitar la inestabilidad fisicoquímica encontrada en algunas suspensiones de liposoma tales como agregación, fusión, hidrólisis, y/o oxidación.

**Objetivo:** el objetivo de esta revisión es centrarse en diferentes aspectos relacionados con los Proliposomas, su método de preparación, técnicas de caracterización, así como señalar su alcance en los sistemas de administración de fármacos.

**Métodos:** los Proliposomas son una nueva forma de sistemas de administración de fármacos. Son productos granulares secos y de flujo libre compuestos por fármacos y fosfolípidos que, al añadirse el agua, se dispersan para formar una suspensión liposomal multilamelar.

**Resultados y discusión:** estos Proliposomas son casi tan buenos o quizás mejores que los liposomas convencionales. En la presente revisión se explica brevemente el concepto de Proliposomas con un enfoque en sus componentes, preparación, caracterizaciones y su campo de aplicación.

**Conclusión:** una extensa encuesta de literaturas y datos recogidos sugiere que los pro-liposomas son portadores de fármacos prometedores para el futuro.

**Palabras claves:** Liposoma; Proliposoma; Estabilidad; Biodisponibilidad; Fosfolípido; Colesterol

#### ABSTRACT

**Background:** For several years, many attempts have been made for the improvement of liposomal stability. In 1986, Payne *et al*, introduced the concept of Pro-liposome for liposome preparation in order to avoid physicochemical instability encountered in some liposome suspensions such as aggregation, fusion, hydrolysis, and/or oxidation.

**Objective:** The objective of this review is to focus on different aspects related to Proliposomes, their method of preparation, characterization techniques and pointing out its scope in drug delivery systems.

**Methods:** Proliposomes are a new form of drug delivery systems. They are dry, free-flowing granular products composed of drug and phospholipid which, upon addition of water, disperse to form a multi-lamellar liposomal suspension.

**Results and Discussion:** These Proliposomes are nearly as good as or perhaps better than conventional liposomes. In the present review attempt has been made to briefly explain the concept of Proliposomes with a focus on its components, preparation, characterizations and their field of application.

**Conclusion:** Extensive survey of literatures and collected data suggests that Pro-liposomes are promising drug carriers for the future.

**Keywords:** Liposome; Proliposome; Stability; Bioavailability; Phospholipid; Cholesterol.

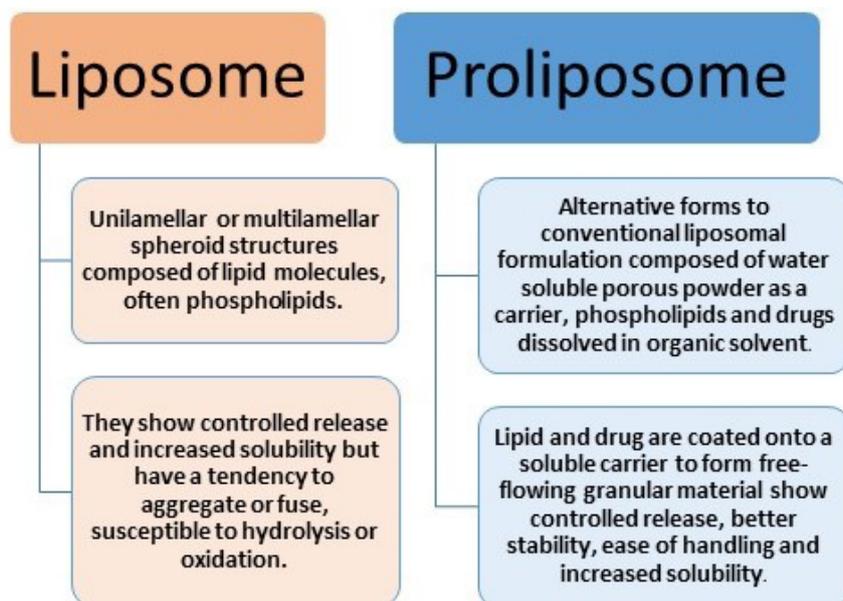
## INTRODUCTION

Liposomes are sphere-shaped vesicles consisting of one or more phospholipid bilayers. Liposomes can trap both hydrophobic and hydrophilic compounds, avoid decomposition of the entrapped combinations, and release the entrapped at designated targets. The liposome can be used as a vehicle for administration of nutrients and pharmaceutical drugs. Additionally, food and farming industries have extensively studied the use of liposome encapsulation to grow delivery systems that can entrap unstable compounds (for example, antimicrobials, antioxidants, flavours and bioactive elements) and shield their functionality. Due to their size and hydrophobic and hydrophilic character (besides biocompatibility), liposomes are promising systems for drug delivery<sup>1,2</sup>. In spite of its broad applications and advantages, liposomes have a problem of degradation by hydrolysis or oxidation as well as sedimentation, aggregation, or fusion with other liposomes in dispersed system during non-lyophilized storage. Other drawbacks associated with the clinical applications of liposomes include difficulties in large-scale production to obtain a product with adequate physical and chemical stability, low solubility, short half-life and sometimes leakage of encapsulated drug/molecules<sup>3,4</sup>. Various approaches have been suggest-

ed to increase the stability of liposomes, including using appropriate lipid compositions, polymer coating, addition of stabilizing lipids to liposomal structures, preparation of double liposomes and proliposomes and some other innovative methods like lyophilization of liposomal solution to stabilize, reconstitute right before use<sup>4,5</sup>. Among all these approaches Proliposome approach is most promising.

The review gives an insight on Proliposomes based approach for the development of a stable liposome and explore its various aspects including its formulation components, preparation, characterization and its potential in drug delivery applications. An extensive literature search was conducted via search engine Google Scholar and databases: PubMed, Science Direct and Springer to summarize the data comprising information on formulation, development, characterization and applications of proliposomes from 80's till date.

Proliposomes are a new type of carrier mediated drug delivery system having many benefits over conventional liposomes. The stability of proliposomes is far superior to liposomes making them more suitable for the delivery of drugs. They are a dry, free-flowing, granular material that immediately forms a liposomal dispersion on contact with water or a biological fluid within the body<sup>5,6,7</sup>. Comparative features of Liposomes and Proliposomes is shown in Figure 1.



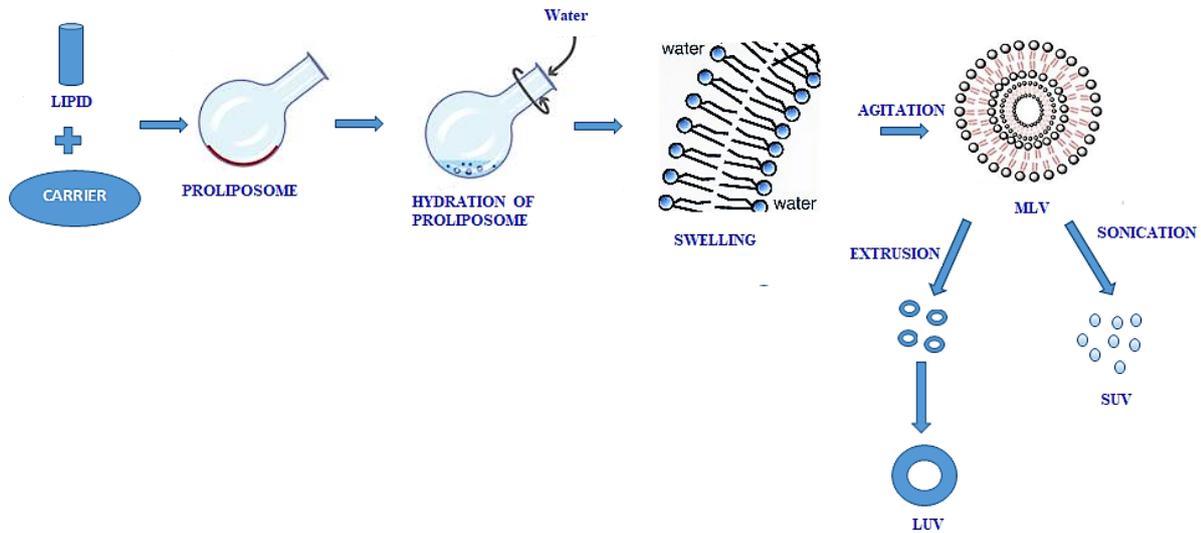
**Figure 1.** Comparisons between Liposomes and Pro-liposomes<sup>14</sup>

The proliposome approach was developed as a simple, reproducible, and reliable manufacturing technique for large-scale production of liposome dispersions. The technology is based upon the intrinsic property of hydrated membrane lipids to form vesicles on contact with water. It involves

layering of the phospholipids onto a finely divided particulate support which results in the formation of dry powders. When the dry powders are hydrated with an aqueous solution followed by gentle mixing, phospholipids on the solid support rapidly disperses to give a liposomal suspension

in an aqueous solution<sup>5,6,7</sup>. Liposomes can either be formed *in vivo* under the influence of physiological fluids or can be formed *in vitro* prior to administration using a suitable hydrating fluid. The liposomes formed on reconstitution

are similar to conventional liposomes and more uniform in size<sup>7,8</sup>. The mechanism of formation of liposome from proliposome is demonstrated in Figure 2.



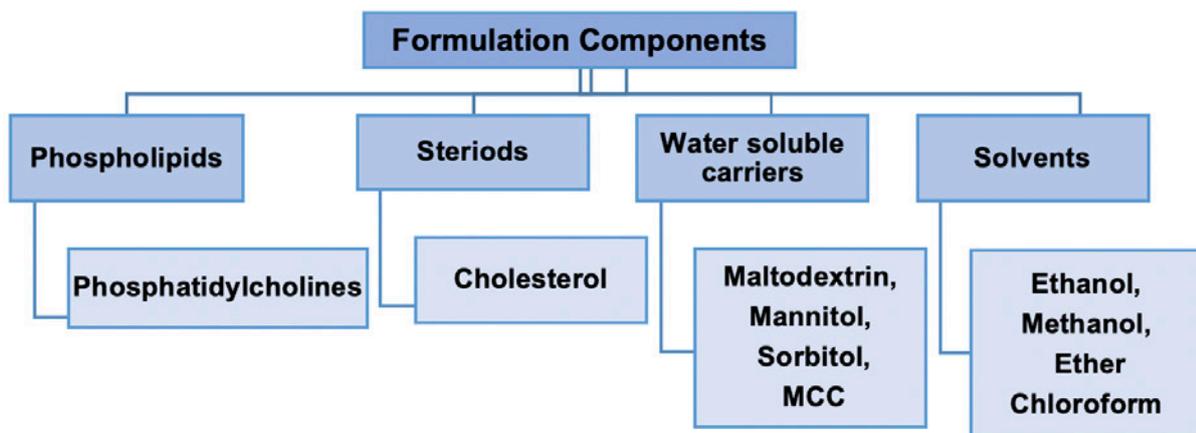
**Figure 2.** Mechanism of formation of Liposomes from Proliposome

Proliposomes have been employed as a basis for a number of site-specific drug delivery approaches. Proliposomal formulations suggest increases solubility and bioavailability of some poorly soluble drugs. Being available in dry powder form, they have an additional convenience in transportation, distribution, storage, processing, packaging,

providing optimal flexibility, unit dosing as capsule and stable during sterilization. All these advantages make them a promising candidate for industrial production. These versatile delivery systems have potential to be used as a carrier for wide range of active compounds<sup>7,9</sup>.

### FORMULATION COMPONENTS FOR PROLIPOSOES

Formulation of proliposomes involves several components:



**Figure 3.** Formulation components for Proliposomes

## Phospholipids

A wide range of lipids are available for the preparation of proliposomes. Phosphatidylcholines (PC) are the most frequently used phospholipids. PCs also known as lecithin can be obtained from natural and synthetic sources. They differ from other amphipathic molecules in the formation of bilayer sheets compared with micellar structures. Natural PCs are commonly derived from egg yolk, soy bean and very rarely from bovine heart and spinal cord. They are typically used as the principal component in proliposomes, due to their relatively low cost, lack of net charge and chemical inertness. Additionally, to PC, neutral lipid bilayers are composed of sphingomyelin (SM). Polar head groups such as phosphatidylglycerol (PG), phosphatidylethanolamine (PE), phosphatidic acid (PA), phosphatidylserine (PS), and Phosphatidylcholines (PC) combined with various fatty acid chains such as oleic, lauryl, myristic, palmitic and stearic acid offering variety of phospholipid structures. In spite of availability of wide variety of phospholipids, preparation of proliposomes is often limited to the family of PCs and PGs, mainly because of toxicological considerations, purity, stability and cost<sup>1,3,4,5</sup>.

## Steroids

Cholesterol and its derivatives are quite often included as components of liposomal membrane. Their inclusion in liposomal membranes has three recognized effects. Increasing the fluidity or micro viscosity, reducing the permeability of the membrane to water soluble molecules and stabilizing the membrane in the presence of biological fluids such as plasma. Its incorporation into phospholipid bilayers causes major changes in their properties. Cholesterol does not by itself form bilayers, but it can be incorporated into phospholipid membranes in high concentrations. It improves the retention of hydrophilic drugs by increasing the rigidity of the bilayers and reducing the permeability, however for hydrophobic drugs it improves encapsulation, only if the drug input is less than the encapsulation capacity of the liposome<sup>10,11,12</sup>.

## Water soluble carriers

The carriers chosen should have high surface area and porosity so that the amount of carrier required can be easily adjusted to support the lipids. It also allows high surfactant to carrier mass ratio within the preparation of proliposomes. Since they are water soluble they allow rapid conversion of liposomal dispersion on hydration and by controlling the size of porous powder, relatively narrow range of reconstituted liposomes can be obtained. Some of the carriers used are- Maltodextrin, Mannitol, Sorbitol, Microcrystalline Cellulose, Magnesium Aluminium Silicates, etc<sup>1,4</sup>.

## Solvents

They are used for providing the softness to vesicle membrane. Most commonly used volatile organic solvent or solvent mixtures are ethanol, methanol, ether and chloroform<sup>13</sup>.

## METHODS FOR PREPARATION OF PROLIPOSOMES

Various methods are available for the preparation of proliposomes. Careful selection of suitable method for a given formulation is essential since various factors such as vesicle size, size distribution, encapsulation capability and retention of contents are affected by the method of preparation. Selection of a given method is based on physicochemical characteristics of the drug, desired type of phospholipid(s), particle size range and ease of preparation. An ideal method of preparation should involve minimal use of organic solvent, avoid long exposure to mechanical stress, employ low temperature and pressure, be reproducible and economical, yield a high drug/lipid ratio and be adaptable for large scale production<sup>1,13,14</sup>.

### a. Film deposition on carrier method

In this method, firstly lipid is mixed with a solid substrate (water soluble carrier) which forms lipid coated solid particles. Upon hydration, solid substrate is dissolved and lipids arrange to form liposomes. Figure 4 A, shows an apparatus for preparing proliposomes by film deposition on carrier method in which an evaporative solution consisting of a solution of drug and phospholipids is added drop by drop by injection through a feed tube onto a core of carrier substance which is carried in a vessel of a rotary flash evaporator under vacuum. At any stated moment, the matrix's over wetting is circumvented and following aliquot of organic mixture is fed slowly when a free-flowing powder matrix is procured. Selected carriers should exhibit great surface area and permeability to regulate the quantity of carrier which is needed to assist the lipids. This also allows great surfactant to carrier mass proportion for the proliposomes production. As they are water soluble, they enable fast production of liposomal dispersion on hydration and by controlling the size of pervious powder, comparatively limited variety of reconstituted liposomes can be obtained. The most commonly used carriers are maltodextrin, sorbitol, microcrystalline cellulose, magnesium aluminium silicates, mannitol, etc<sup>14</sup>.

### b. Spray drying method

This method is mainly used when particles of uniform size and shape are required and can be easily scaled up in a cost effective way that is suitable for large scale production of proliposomes. The unique feature of spray drying process

lies in its ability to involve both particle formation and drying in a continuous single step, allowing better control of particle. Spray drying is not only limited to aqueous solutions, but can also be used for non-aqueous systems to prepare particles. Figure 4 B shows the various stages involved in spray drying process. Firstly, liquid dispersions carrying pure lipid or lipids and carriers in organic mixture is prepared and then the dispersion is poured into a dry cell. Dispersions are atomized in the drying cell utilizing a spray nozzle and desiccated in a simultaneous air flow which is then collected in a tank <sup>15</sup>.

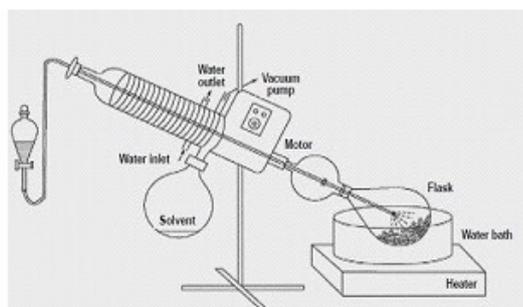
#### c. Fluidized bed method

Fluidized bed method is used for the large scale production of proliposomes. Apparatus for preparing proliposomes by Fluidized bed method is shown in Figure 4 C. This method is based on the principle of particle coating technology. Here, carrier material can vary from crystalline powder to non pareil beads. When non pareil beads are used as carrier material, first pareil beads are coated with seal coating to get smooth surface which can help further in coating of phospholipids and also ensure thin uniform coating formation of phospholipids around the core and small sized liposomes upon hydration. Carrier material sprayed with the solution of organic solvent and solution of drugs through nozzle. At the same time, organic solvent is removed by applying vacuum to the fluid bed. The trace

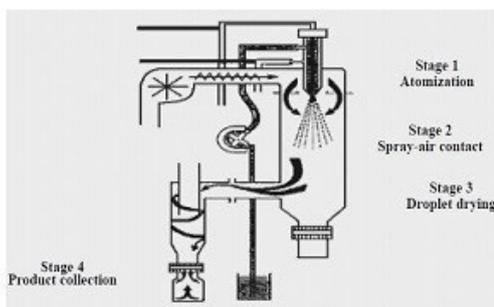
amount of residual solvent is removed from the finished lipid-coated powder/beads when dried under vacuum overnight <sup>9,16</sup>.

#### d. Supercritical anti-solvent method

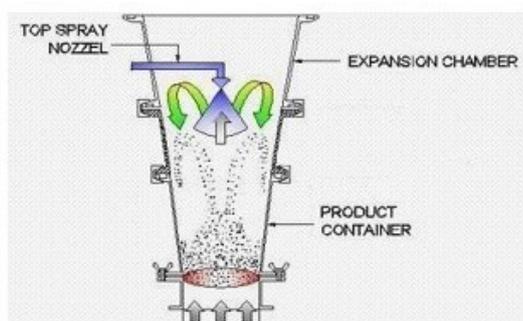
Supercritical anti-solvent method utilizes Supercritical Carbon dioxide (SCCO<sub>2</sub>) in the preparation of proliposomes. SCCO<sub>2</sub> is a fluid state of carbon dioxide where it is held at or above its critical temperature and pressure. The apparatus used in the preparation of proliposomes include following parts (See Figure 4 D): CO<sub>2</sub> syringe pump; circular and cooling lines for maintaining the CO<sub>2</sub> pump head and CO<sub>2</sub>, which flowed out of a storage tank (-7°C); and a reaction vessel containing a magnetic stirrer, pressure indicator, and temperature indicator. Firstly, a clear and homogenous solution of phospholipids, cholesterol and drug is prepared. The drug-lipid solution and carrier material is then sealed in the reaction vessel. The supercritical CO<sub>2</sub> pumped to the vessel by a syringe pump. After approximately 30 minutes of stirring at equilibrium, additional supercritical CO<sub>2</sub> continued to flow into the vessel for about 30 minutes to wash out any remaining solvents. The vessel is then slowly depressurized to atmospheric pressure, and drug-phospholipid mixture coated the surface of carrier particles, forming a thin film. SCF mediated pro- liposomes is then collected and stored at 4°C <sup>16,17,18</sup>.



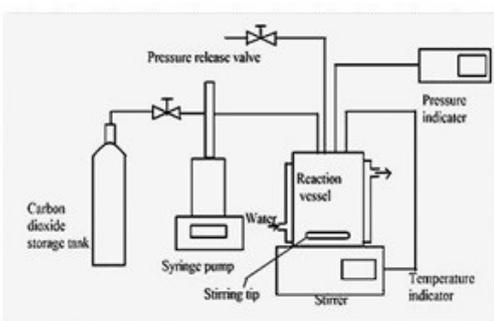
(A) Film deposition on carrier method



(B) Spray drying method



(C) Fluidized bed method



(D) Super critical anti-solvent method

Figure 4. Apparatus for preparation of Proliposomes

## CHARACTERIZATION OF PROLIPOSOMES

Proliposomes are characterized for morphology, angle of repose, rate of hydration, penetration and permeation studies.

### Particle size

Particle size of proliposome is a very important characteristic. Size distribution and surface morphology (smoothness, roundness and aggregates formation) of particles can be studied by scanning electron microscopy (SEM). The deposition of phospholipid on the carrier material is confirmed by illegibility of the image of the carrier material in the formulation of proliposomes<sup>19</sup>.

### Hydration Study and Vesicle formation

It is important to determine the formation of liposomal vesicle following hydration of the proliposomal formulation *in vitro*. The vesicle formation by the particular procedure can be confirmed by optical microscopy. The liposome suspension has to be placed over a glass slide and dried at room temperature, the dry thin film of liposome suspension formed has to be observed for the formation of vesicles<sup>6,14</sup>.

### Measurement of zeta potential

Another characteristic of proliposomes is zeta potential that is of extreme interest. It is a measure of the particle charge, the larger the zeta potential absolute value the larger the amounts of surface charge. Logically, the zeta potential is an index for particle stability. A physically stable proliposomal formulation solely stabilized by electrostatic repulsion will have a  $\pm 30\text{mV}$  of minimum zeta potential and this stability helps in preventing aggregation<sup>20</sup>.

### Separation of untrapped drug

Free or untrapped drug can be separated by centrifugation of liposomal suspension, the pellets and supernatant are separated. The obtained pellets are washed and then resuspended to obtain a liposomal suspension free from untrapped drug.

Gel filtration is another method used for separation of untrapped drug from liposomal dispersion using a Sephadex-G-50 column, eluted with suitable mobile phase and analysed with suitable analytical techniques<sup>2,21</sup>.

### Differential Scanning Calorimetry and Powder X-ray Diffractometry

Differential scanning calorimetry (DSC) and powder X-ray diffractometry (PXRD) can be used to determine the solid state properties of drug after formulating in to prolipos-

omes i.e., changes in its form from crystalline to amorphous. This is especially important when the drug's solubility was improved using proliposomal formulation<sup>22</sup>.

### Flow Properties

Flow properties mainly explain content uniformity and handling processing operations and also ease filling. Since it is a solid powder based formulation, it is important to analyse the flow properties in order to translate them into a convenient dosage forms such as tablets or capsules. Flow properties can be assessed by measuring the parameters such as bulk density, tapped density, angle of repose, Carr's compressibility index and Hausner's ratio<sup>23</sup>.

### Determination of entrapment (entrapped) efficiency

Entrapment efficiency is carried by hydrating the proliposomes to form liposome dispersion followed by separation of untrapped drug and determining the amount of drug entrapped. Untrapped or free drug can be separated by using any one of the method described above<sup>24,25</sup>.

### In vitro drug release from proliposomes

*In vitro* drug release studies for proliposomes can be done by various techniques such as USP dissolution apparatus Type I, Franz diffusion cell, dialysis tubing, reverse dialysis, cellophane dialyzing membrane, keshary-chien diffusion cell and spectrapormolecular porous membrane tubing.

*In vitro* skin permeation studies can be carried out using flank skin, dorsal skin of albino rabbit, female albino rat (Sprague-Dawley strain), Wistar rat skin (7-9 weeks old)<sup>2,7, 21,23,26,27</sup>.

### Stability studies

The stability studies can be performed by storing the samples at different temperatures like freezing temperature (2-8°C), room temperature (25±0.5°C) and higher temperature (45±0.5°C) for a period of 1-3 months. Periodically, drug content and difference in the average vesicle diameter can be observed. According to ICH guidelines, dry proliposome powder meant for re-formulation should be considered for accelerated stability at relative humidity 75%/40°C as per international climatic conditions and zones. Long-term stability studies have to be conducted based on the climatic zones of the countries. Temperature and relative humidity to be maintained for zones I & II and III & IV are 25°C/60% RH and 30°C/65% RH, respectively. The product should be evaluated for appearance, surface characteristics, drug content, color change, pH, particulate matter, assay, preservative content, pyrogenicity and sterility<sup>2,21,28</sup>.

## APPLICATION OF PROLIPOSOMES IN DRUG DELIVERY

Proliposomes have been studied for various routes of administration including oral, transdermal, mucosal, nasal, ocular, pulmonary and parenteral. Proliposomes derived liposomes showing advantages as drug carriers, comprising lower cost and toxicity, easy storage and handling and increased stability. Various applications of proliposomes are shown in Table 1.

### Proliposome in Oral delivery

Oral drug delivery continues to be the preferred route of administration, but liposomes have limited success in delivering drugs through oral route due to a lack of stability, erratic and unpredictable absorption profiles. Being available as a free flowing powder, Proliposomes represent the first example of delivering liposomes into solid dosage form such as tablets or capsules. Further, liposomes are formed on contact with biological fluids at the site of absorption ensuring the retention of liposome integrity<sup>29</sup>. Domperidone is a specific 5HT<sub>3</sub> receptor antagonist used in the treatment of nausea and vomiting. It has low aqueous solubility and moreover after oral administration it undergoes extensive gastric and hepatic first pass metabolism. Dhurke *et al*, made an attempt to develop proliposomes of domperidone with an aim to improve bioavailability by increasing intestinal permeability which would transport drug through the lymphatic transport system and bypassing first pass metabolism<sup>30</sup>. Chuandi *et al*, investigated the possibility of liquid proliposomes being carriers for oral delivery. They prepared liquid proliposomes based on soft capsules of Nimodipine and reported that proliposomes show improved oral delivery of Nimodipine<sup>31</sup>. Proliposomes could also be a useful vehicle for oral delivery of dehydrosilymarin, a poorly soluble drug in water. Chu *et al*, prepared proliposome of dehydrosilymarin with a polyphase dispersed system consisting of soybean phospholipids, cholesterol, isopropyl myristate and sodium cholate. Dehydrosilymarin proliposomes prepared by a film dispersion-freeze drying showed improved oral bioavailability of dehydrosilymarin<sup>29</sup>.

### Proliposome in Transdermal delivery

Phospholipids, being the main component of liposomal system, will simply get integrated with the skin lipids and maintain the desired hydration conditions to enhance drug permeation. When proliposomes are applied to the mucosal membrane, they are expected to form liposomes on contact with mucosal fluids whereby the resulting liposomes act as sustained release dosage form for loaded drugs. Liposomes formed on hydration can modulate diffusion across

the skin<sup>32,33,34</sup>. Several investigations have been made to examine the feasibility of proliposomes as a sustained transdermal dosage form. Hwang *et al* prepared proliposomes containing varying amounts of Nicotine using sorbitol and lecithin<sup>35</sup>. In the investigation made by Shruthi *et al* it was found that proliposomal gel of transdermal Metformin hydrochloride allows delivery of drug through the skin with significant reduction of glucose level<sup>14</sup>. Kumara *et al* prepared proliposomal gel system of Repaglinide to deliver the drug over an extended period for the treatment of type - 2 diabetes mellitus. Results obtained confirmed proliposomes was a better choice for controlled release of drug through topical drug delivery<sup>36</sup>. Diwan *et al*, prepared proliposomal gel of Prednisolone, a steroidal anti-inflammatory agent intended for topical application and reported that Prednisolone proliposomal gel showed sustain release with enhanced anti-inflammatory activity indicating its potential role in the treatment of rheumatoid arthritis<sup>37</sup>. Kurakula *et al*, prepared proliposomal gel bearing a non-steroidal anti-inflammatory agent Piroxicam for topical application. Piroxicam proliposomal gel showed sustain release with enhanced anti-inflammatory activity<sup>38</sup>.

### Proliposome in Mucosal delivery

Proliposomes form vesicular structures (liposomes) *in vivo*, triggered by the aqueous environment found on the mucosal surfaces. Phospholipids present in them have a natural affinity for biological membranes. The presence of drug as molecular dispersion in the bilayers offers improved drug activity. Further, the difficulties associated with liposomal preparations such as stability and loading are circumvented because the proliposomes convert to vesicular structures *in vivo*, i.e., on the mucosa<sup>39,40</sup>. Ning *et al*, developed Clotrimazole(CT)-containing vaginal proliposomes for prolonged drug release that increases the amount of drug retention into the mucosa which resulted in increased antifungal efficacy<sup>39</sup>.

### Proliposome in Ophthalmic delivery

Ocular drug delivery is challenging in terms of achieving optimum drug concentration due to unique protective mechanisms of the eye. Development of a drug delivery system for attaining therapeutic concentration at the target site requires a comprehensive understanding of static and dynamic barriers of the eye<sup>41</sup>. Liposomes have been investigated for ophthalmic drug delivery as they offer advantages as a carrier system. They are biodegradable and nanocarriers. They can enhance the permeation of poorly absorbed drug molecules by binding to the corneal surface and improving residence times. Karn *et al*, developed a dry proliposome containing Cyclosporin A for use in the treat-

ment of several autoimmune, parasitic diseases and various inflammatory ocular surface disorder <sup>42</sup>.

### Proliposome in Pulmonary delivery

Proliposomes have been shown to be very promising in the delivery of various types of pulmonary drugs <sup>43</sup>. Rojanarat *et al*, designed Levofloxacin (LEV)- proliposomes in a dry powder aerosol form for pulmonary delivery. LEV-proliposomes were less toxic to the respiratory-associated cells than LEV, and did not activate AMs (Alveolar macrophages) to produce inflammatory mediators. The efficacy of LEV-proliposomes against *M. bovis* was significantly higher than that of free LEV <sup>44</sup>. Patil *et al*, prepared Rifapentine loaded proliposomes for the treatment of tuberculosis by spray drying method and independent variables were optimized using a factorial design approach<sup>45</sup>. Kajornwongwattana *et al*, prepared proliposome powders containing isoniazid (INH) in a dry powder aerosol form and studied for its toxicity to respiratory-associated cell lines and its potential to provoke immunological responses from alveolar macrophages (AM). Free INH and INH-proliposome bioactivities were tested *in vitro* and in alveolar macrophages infected with *Mycobacterium bovis* (*M. bovis*). INH-proliposome exhibited better antimycobacterial activity against *M. bovis*-infected AM. Results obtained indicates INH-proliposomes are potential candidates for an alterna-

tive tuberculosis treatment <sup>46</sup>. Pulmonary liposomal delivery system of budesonide was prepared and evaluated for sustained release <sup>47</sup>. Liposomal formulation of salbutamol in dry powder form was also developed as sustained release systems for the pulmonary delivery<sup>48</sup>.

### Proliposome in Nasal delivery

Nasal drug delivery has received a significant attention in recent years as a convenient and reliable route, not only for local but also for the systemic administration of drugs. Proliposomes have also shown their potential in nasal drug delivery. They provide combined advantage of a fast onset (surface drug) and prolonged drug action (encapsulated drug) <sup>49,50</sup>. Jung *et al*, performed to achieve prolonged delivery of nicotine to the systemic circulation. Proliposomes containing nicotine base (NB-proliposomes) or nicotine hydrogen tartrate salt (NS-proliposomes) and a mixture of powdered nicotine hydrogen tartrate salt and sorbitol (1:9 mixtures, MP) were administered intranasally to rats at a nicotine dose of 1 mg/kg and reported prolonged delivery of nicotine to systemic circulation<sup>51</sup>. In another interesting study free flowing proliposomes containing propranolol hydrochloride (PH) were evaluated by Jung *et al*, for their potential as a nasal drug delivery system to sustain the plasma concentration of the drug <sup>52</sup>.

**Table 1.** Some of the research work carried out on proliposome as drug carriers

S. No.	Route	Drug	Application	References
1	Oral	Domperidone	Proliposomes	30
2	Oral	Nimodipine	Proliposome based soft capsule	31
3	Oral	Silymarin	Proliposome	29
4	Transdermal	Nicotine	Proliposomal gel	35
5	Transdermal	Metformin hydrochloride	Proliposomal gel	14
6	Transdermal	Repaglinide	Proliposomal gel	36
7	Transdermal	Prednisolone	Proliposomal gel	37
8	Transdermal	Piroxicam	Proliposomal gel	38
9	Mucosal	Clotrimazole	Vaginal proliposomes	39
10	Ophthalmic	Cyclosporine	Dry proliposomes	42
11	Pulmonary	Levofloxacin	proliposomes in a dry powder aerosol	44
12	Pulmonary	Isoniazid	Proliposome powder	46
13	Nasal	Nicotine	Proliposomes	51
14	Nasal	Propranolol HCl	Proliposomes	52
15	IV	Ibuprofen	Proliposomes	53
16	IV	Amphotericin B	Proliposomes	6
17	IV	Methotrexate	Proliposomes	54

## CONCLUSIONS AND FUTURE PERSPECTIVES

Pro-liposomes are promising drug carriers for the future. They have provided a major breakthrough in solving the stability, bioavailability and solubility of poorly soluble drugs issues associated with liposomes and they offer a non-invasive delivery of drug into or across the skin. They are better alternative to the liposomal vesicular system due to their greater physical, chemical stability and potentially scalable for commercial viability. Since they are dry powder form they are suitable for preparing unit dosages forms such as tablets, capsules and beads etc. Owing to all these advantages pro-liposomes has been used for broad range of pharmaceutical application. Proliposomes are administered orally, parenterally, topically as well as used in cosmetic and hair technologies, sustained release formulations, diagnostic purpose and as good carriers in gene delivery. Proliposomes are becoming a useful drug carrier for different delivery systems. Still there is a need for discovering the new delivery systems using proliposomes in the field of nutraceuticals, herbal actives and other synthetic formulations. Hence, a wider research should be done to develop scale-up batches for drug and natural preparations

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