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Exploring Proliposomes: A Review of Advanced Pharmaceutical Carrier Drug Delivery Systems

Praji SP[1], Deepa Manohar R[2], Mathan S[3], Shaiju S Dharan[3], Shiji SP[3].
Department of Pharmaceutics, Ezhuthachan College of Pharmaceutical Sciences, Marayamuttom, Thiruvananthapuram, Kerala.

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ABSTRACT
Liposomes are a microscopic vesicle, consist of bilayer of phospholipid serves as an innovative novel drug delivery system, releasing drug at a predetermined rate. But it has a challenge in storage due to its poor stability issues. Inorder to overcome the stability problem payne et al in 1986, introduced concept of Proliposomes. Proliposomes are new form of novel drug delivery system are better than conventional liposomes and in contact with water disperse to form liposomal suspension. Proliposomes are dry, free-flowing, granular substance which come in contact with water or biological fluid disperse to form liposomal suspension. They Significantly enhanced addressing stability, bioavailability, and solubility challenges of poorly soluble medicines related to liposomes through non-invasive drug administration on or through the skin. They are alternative to the liposomal vesicular system. They are available in dry powder form. Having most of the advantages they can be used for various therapeutic applications.

KEYWORDS: Proliposomes, liposomes, Drug delivery system, poorly soluble,Vesicular System, Phospholipids, Water Soluble Carriers.

I. INTRODUCTION

"Lipos" derived from the Greek word for fat, and "soma," meaning body, form the basis of the term "liposome". In comparison with other novel delivery system, liposomes are considered to be effective, well researched and widely used. Liposomes are micro spherical vesicle consist of phospholipid molecules which enclose aqueous core[1]. It can serve as a delivery system for pharmaceuticals and nutrients. Drug compound can be incorporated into either the lipid bilayer or the aqueous phase. They can encapsulate both hydrophobic and hydrophilic substances, preventing the breakdown of the encapsulated mixtures and releasing them at specified targets[2]. They show promise as drug delivery systems due to their size, hydrophobic and hydrophilic attributes and biocompatibility. They can serve as carriers for delivering both nutrients and pharmaceutical drugs.Although liposomes offer numerous uses and advantages, they are susceptible to oxidation, hydrolysis, sedimentation, aggregation, or fusion with other substances. Liposomes exhibit instability as colloidal structures due to their physical and chemical characteristics, may have short shelf life and sometimes leakage of encapsulated drug/molecule[3]. Enhancing liposome stability can involve employing appropriate lipid compositions, polymer coating, the addition of stabilizing lipids to liposomal structures, the preparation of double-liposomes and proliposomes, as well as some other cutting-edge techniques like lyophilizing liposomal solution to stabilize and reconstitute just before use. To tackle liposomal stability issues, a novel proliosomes approach is the best which has been developed, enabling rapid on-demand liposome formation with minimal manipulation[4].

Proliposomes stand as an innovative carrier-mediated drug delivery system, offering several advantages over traditional liposomes. Notably, proliposomes demonstrate significantly improved stability compared to liposomes, rendering them a preferable choice for drug delivery. These are dry, easily flowing granules that swiftly form a liposomal dispersion upon encountering water or biological fluid within the body. They comprise a water-soluble porous powder and phospholipid. The proliposomes approach was developed as a simple, repeatable technique for large-scale production of liposomal dispersions.It includes depositing phospholipids onto finely divided particulate support, leading to the creation of dry powders[6]. Phospholipids on a solid substrate disperse rapidly when hydrated with

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an aqueous solution, forming a liposomal suspension through gentle mixing in water. Liposomes can be generated either in-vivo influenced by physiological fluids or in-vitro before administration using an appropriate hydrating fluid. Liposomes formed upon reconstitution resemble conventional liposomes and exhibit a more uniform size distribution[7].

In the production of commercial liposome products, pro-liposome stands out as one of the most widely used and cost-effective methods. Proliposomes have been utilized as a foundation for several site-specific drug delivery strategies. They can enhance solubility and bioavailability of some poorly soluble drugs[8]. As they are available in powder form, they can enhance transportation, distribution, storage, processing, packaging, providing optimal flexibility, unit dosing as capsule and stable during sterilization. Indeed, versatile delivery systems offer the potential to effectively transport a diverse array of active compounds, expanding their applicability across various industries and fields[9].

COMPARISON OF PROLIPOSOMES WITH LIPOSOMES

Proliposomes were scaled up to produce liposomal dispersion on a large scale. The mechanism involves the intrinsic property of hydrated membrane lipids to form vesicles upon contact with water[10].

Properties	Proliposomes	Liposomes
Structure and Composition	Create alternative liposomes by using water soluble porous powder as a carrier, incorporating phospholipids and dissolving drugs in an organic solvent[3].	Unilamellaror multilamellar spheroidstructures composed of Phospholipid, cholesterol and aqueous phase[11].
Physical form	Lipid and drug are applied to a soluble carrier, creating a free-flowing substance[6].	They exist in the form of an aqueous dispersion[12].
Stability	Improved stability, ease of handling and increased solubility[3].	Increased solubilty due tooxidation[13]
Release	Controlled release$_{14}$	Controlled release[11]
Aggregaation	No aggregation or fusion of liposomes[6].	Tends to aggregate and fuse[15]
Oxidation and Hydrolysis	Lowers oxidation and hydrolysis[3].	Prone to hydrolysis and oxidation[16]

Table 1: Comparison of proliposomes with liposomes

ADAVANTAGES OF PROLIPOSOMES

- Proliposomes aim to improve bioavailability and protect drugs from degradation in the gastrointestinal tract[17].
- Directing anticancer drugs to specific tumor sites for targeted treatment.
- Alteration of phospholipid composition in bilayers allows for controlled release within the vasculature.
- Decrease toxicity and mask taste[18].
- Enhanced therapeutic index and efficacy.
- Improved stability through encapsulation prevents over loading[19].
- They are employed for precise drug delivery and regulated release.

FACTORS AFFECTING PROLIPOSOME FORMULATION

1. Total lipid concentration:

Increasing lipid concentration correlated with a rise in the drug's percentage encapsulation efficiency. The percentage encapsulation efficiency of the medication exhibited a linear with the total lipid concentration[20].

2. Drug concentration:

Higher drug concentrations in proliposomes showed enhanced encapsulation efficiency and increased drug content per mole[21].

3. Charge of lipids

The addition of diacetyl phosphate (DCP), introducing a negative charge, or stearyl amine (SA), inducing a positive charge, resulted in a decrease in the percentage of drug encapsulation efficiency within the lipids[22].

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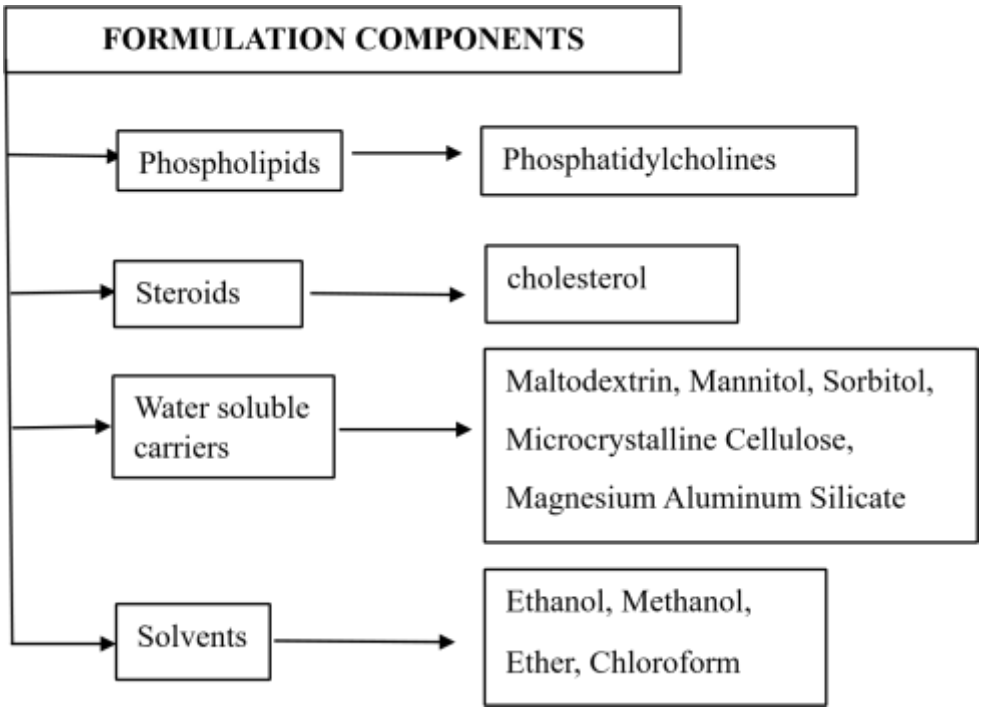
4. Impact of the phosphatidylcholine (PC) to cholesterol ratio:

Different ratios of phosphatidylcholine (PC) to cholesterol in proliposomes yield varying percentages of drug entrapment efficiencies (EE%). Incorporating more cholesterol within a constant molar ratio range results in higher EE%. Cholesterol, a crucial factor in proliposomal and liposomal formulations, enhances entrapment efficiencies. While cholesterol integrates into phospholipid bilayers and contributes to their structure, excessive amounts can impede drug molecule partitioning, reducing encapsulation. Increasing cholesterol concentrations significantly enhance entrapment efficiencies in all proliposomal formulations. Cholesterol's rigidifying effect in the fluid crystal state aids vesicle creation, positively impacting entrapment efficiency. Without this influence, encapsulation efficiency would decrease[23].

5. Effect of total lipid-to-sorbitol ratio:

Comparing total lipid:sorbitol ratios of 1:10 and 1:20 revealed that sorbitol concentration has no significant impact on the encapsulation efficiency (EE%) of cholesterol. However, when the total lipid-to-sorbitol ratio exeeds 1:10, the preparation of proliposomes becomes challenging. The spraying-evaporating process takes significantly longer due to the limited volume of the solution that can be injected and sprayed onto the small amount of sorbitol at a time. A sorbitol concentration of 1:10 was chosen for proliposomes manufacturing, as higher concentrations did not enhance the formation process[1].

COMPONENTS OF PROLIPOSOMES FORMULATION



Phospholipids:

A diverse range of lipids, notably phosphatidylcholines (PC), are commonly used in proliposome preparation. PCs, also known as lecithin, can be sourced from natural (e.g., egg yolk, soybean) or synthetic origins. These amphipathic molecules form bilayer sheets distinct from micellar structures. Natural PCs are frequently derived from egg yolk, soybean, and occasionally bovine heart/spinal cord, serving as the primary component in proliposomes due to their cost-effectiveness, lack of net charge, and chemical inertness[9]. Additionally, neutral lipid bilayers include sphingomyelin (SM) along with polar head groups like phosphatidylglycerol (PG), phosphatidylethanolamine (PE), phosphatidic acid (PA), and phosphatidylserine (PS), combined with various fatty acid chains (oleic, lauryl, myristic,

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palmitic, stearic acid), providing diverse phospholipid structures. Despite a wide array of phospholipids, proliposome preparation is often limited to phosphatidylcholines and phosphatidylglycerol families, primarily due to considerations of toxicity, purity, stability, and cost[24].

Steroids

Cholesterol and its derivatives are commonly added to liposomal membranes, influencing fluidity, reducing permeability to water-soluble molecules, and enhancing stability in biological fluids. Their inclusion brings about significant changes in the properties of phospholipid bilayers. While cholesterol doesn't form bilayers alone, it can be integrated into phospholipid membranes at high concentrations. This incorporation enhances the rigidity of bilayers, reducing permeability and improving the retention of hydrophilic drugs. For hydrophobic drugs, it enhances encapsulation, but only when the drug input is below the liposome's encapsulation capacity[25].

Water soluble carrier:

The chosen carriers should possess substantial surface area and porosity for easy adjustment of the required amount to support lipids. This facilitates a high surfactant to carrier mass ratio in proliposome preparation. Being water-soluble, these carriers enable swift conversion of liposomal dispersion upon hydration.Through the regulation of the porous powder's size, it becomes feasible to attain a relatively restricted spectrum of reconstituted liposomes. Common carriers include Maltodextrin, Mannitol, Sorbitol, Microcrystalline Cellulose, and Magnesium Aluminium Silicates[5].

Solvent:

Solvents are employed to impart softness to vesicle membranes. The most commonly used volatile organic solvents or solvent mixtures include ethanol, methanol, ether, and chloroform[24].

METHODS OF PREPARATION

Various methods can be used to prepare proliposomes, and the choice depends on factors like vesicle size, size distribution, encapsulation capability, and content retention. Selecting the appropriate method is crucial, considering the physicochemical characteristics of the drug, preferred phospholipid type, particle size range, and ease of preparation. Ideally, the method should minimize organic solvent usage, reduce exposure to mechanical stress, involve low temperature and pressure, be reproducible, cost-effective, yield a high drug/lipid ratio, and be suitable for large-scale production. Methods include[1]:

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

Film deposition on carrier method

Pro-liposomes are created through the film deposition on a carrier technique, involving a water-soluble carrier material for medication and phospholipid coating. A feed tube drops an evaporative solution onto a rotating flash evaporator with a carrier substance core. In this method, lipids are initially mixed with a water-soluble solid substrate, forming lipid-coated solid particles. Upon hydration, the solid substrate dissolves, and lipids arrange to form liposomes. The process involves film deposition on a carrier using an evaporative solution of drug and phospholipids. Chosen carriers with large surface area and permeability enabling a high surfactant to carrier mass ratio control the amount needed to support lipids[26]. Maltodextrin, sorbitol, microcrystalline cellulose, magnesium aluminum silicates, mannitol, etc., are frequently employed as carriers.

Slow incorporation and evaporation steps of the solvent can be addressed by spreading the carrier substance in an organic medicine and phospholipid mixture in a rotary evaporator vessel before vacuum evaporation[27]. This alternative method results in a highly ordered and constant lipid dispersion, providing a stable procedure that takes less time than the original process. The unique reclining propensity of the spray drying method sets it apart[28].

Spray drying method

This process stands out for its ability to seamlessly combine particle composition and drying, ensuring a consistent stride for more optimal particle production. It is versatile, applicable to both aqueous and non-aqueous systems. Primarily employed for uniform-sized and shaped particles, it is easily scalable. The cost-effectiveness makes it suitable for largescale preparation of Proliposomes[29].

The spray drying process involves four phases: atomization of the product through a spray nozzle, spray-air association, drying of the spray

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droplets, and collection of the solid product. Liquid dispersions with pure lipid or lipids and carriers are prepared, poured into a dry cell, atomized using a spray nozzle, and desiccated in a simultaneous airflow, ultimately collected in a tank. Crucial factors influencing this method involve elevated temperatures, shearing stresses, and absorption events, potentially resulting in thermal and mechanical degradation of active molecules. Improvements can be made by optimizing working variables such as drying air temperatures and liquid spraying rate. To protect active molecules, stabilizing adjuvants like disaccharides, cyclic oligosaccharides, and polyols can be used, while increasing the surface area of lipids enhances hydration effectiveness[30].

Supercritical anti-solvent method

In the production of phospholipids (PLs), we employ the supercritical anti-solvent method utilizing Supercritical Carbon Dioxide (SCCO2), which is essentially carbon dioxide in its fluid state maintained above its critical temperature and pressure. Main three factors involved are Lower residual solvents, Simple steps, Mild operation temperature[31].

To prepare phospholipids (PLs) using anti-solvent technology, a three-part apparatus is employed, comprising a sample delivery unit, precipitation unit, and separation unit. Two pumps, one delivering CO_2 from a cooled cylinder with the use of refrigerator ($72cm^3$) and the other introducing drug solutions via a high-pressure pump connected to buffer tank (7℃), for preheating, ensures that the reaction vessel or CO_2 cylinder maintains conditions at 45℃ and 10MPa, while the drug solutions introduced via the HPLC combined to form the sample delivery unit. Organic solvents miscible with CO2 dissolve phospholipids, cholesterol, and drugs to obtain clear and homogeneous solution followed by sonication. For entry of CO2 into vessel through nozzle valve A and B are opened[19].CO_2 sprayed to outer tubule and the solution are sprayed through inner tubule of nozzles into a vessel. The second part of the apparatus has three parts: a vessel heated by air, a wet gas meter, and a separator. The separator isolates CO2 from the organic solvent due to low pressure[32]. Once the temperature and pressure reach the preset values, valve A opens allowing CO2 to enter. Subsequently, valve B permits the drug solution to enter the nozzle, where it swiftly mixes with $SCCO_2$ and diffuses rapidly, akin to being sprayed through a coaxial nozzle. The solute rapidly dissolves in the organic solvent, achieving supersaturation within approximately 30 minutes. This occurs as the solute's solubility in the organic solvent gradually decreases, leading to the precipitation of PLs in the vessel. Upon utilizing the solution entirely, valve A and B are sealed, and valve C is opened to depressurize the vessel at the designated temperature. Ultimately, the collected samples at the vessel's bottom on the filter are obtained, with the need for optimizing pressure, temperature, and drug solution flow rate for achieving high drug loading in PLs[33].

Fluidized bed method

This process employs particle coating technology, transitioning from crystalline powder to nonpareil beads as the carrier material. The beads serve as the initial carrier, receiving a seal coating to create a smooth surface for subsequent phospholipid coatings. This leads to the formation of a thin, consistent coating of phospholipids surrounding the core, resulting in the creation of smaller-sized liposomes upon hydration.material occurs through a nozzle. Meanwhile, the organic solvent is removed by applying a vacuum to the fluid bed. To eliminate residual solvent traces, the finalized lipidcoated powder or beads can undergo overnight drying under vacuum[34].

CHARACTERIZATION OF PROLIPOSOMES

Particle size

Particle size is a very important factor in evaluating existence of proliposomes. With the help of Digital optical microscope, size distribution of particle can be studied[22]. The confirmation of phospholipid deposition on the carrier material is indicated by the illegibility of the carrier material image in proliposome formulation[35].

Surface morphology

Scanning electron microscopy is employed as a method for assessing the surface morphology of proliposomal powder[23]. This technique provides insights into the carrier's structure post-lipid coating, aiding in the comprehension of the porous surface characteristics before and after the deposition of the proliposomal formulation[36].

Surface charge:

Zeta potential serves as a gauge for particle charge, with a higher absolute value indicating increased surface charge. Logically, it acts as an indicator of particle stability[37]. A physically stable proliposomal formulation, relying

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on electrostatic repulsion, maintains a minimum zeta potential of ±30mV, contributing to the prevention of aggregation[38].

Hydration study:

Confirming the formation of liposomal vesicles post-hydration of proliposomal formulation in vitro is crucial. Optical microscopy can validate vesicle formation through a procedure where the liposome suspension is dried on a glass slide at room temperature. The resulting dry thin film of liposome suspension is observed for the presence of vesicles[39].

Flow property:

Flow properties play a crucial role in ensuring content uniformity, facilitating processing operations, and easing filling. For solid powder-based formulations like tablets or capsules, analysing flow properties is essential[28]. Parameters such as bulk density, tapped density, angle of repose, Carr's compressibility index, and Hausner's ratio are measured to assess these flow properties[40].

Drug Content

The drug quantity in proliposomal formulations can be assessed through various techniques. Ideally, for a poorly soluble drug, 100% of it should be in the lipid phase due to their solubilized state. While determining drug content in proliposomal powder, it's expected to be 100%[30]. However, literature often reports 'encapsulation' or 'entrapment' efficiency due to potential separation of drug during coating or proliposome hydration[41]. Techniques like dialysis or centrifugation are used to estimate the amount of free drug. When using 'encapsulation' or 'entrapment,' it signifies the drug is enclosed within lipid bilayers after proliposomes hydrate into liposomes. Can be analysed by UV-visible spectrophotometer[42].

Separation of unentrapped drug:

Centrifugation of liposomal suspension separates the free or unentrapped drug, with pellets and supernatant isolated[43]. The pellets are washed and subsequently resuspended, yielding a liposomal suspension devoid of unentrapped drug. Gel filtration, employing a Sephadex-G-50 column, is employed to separate unentrapped drug from liposomal dispersion. The elution is conducted with a suitable mobile phase, and the analysis is carried out using appropriate analytical techniques[44].

Determination of entrapment efficiency:

The assessment of entrapment efficiency involves hydrating proliposomes to form a liposome dispersion, followed by the separation of unentrapped drug and quantification of the amount of drug entrapped within the liposomes[35]. Any of the previously mentioned methods can be employed to separate untrapped or free drug[42].

Stability studies

Stability studies involve storing samples at various temperatures (2-8ºC, 25±0.5ºC, and 45±0.5ºC) for 1–3 months. Periodic observations of drug content and average vesicle diameter changes are recommended[33]. Following ICH guidelines, dry proliposome powder intended for reformulation undergoes accelerated stability testing at 75%/40ºC[45]. Long-term stability assessments align with climatic zones, requiring maintenance of specific temperature and humidity conditions (25ºC/60% RH for Zones I & II and 30ºC/65% RH for Zones III & IV). Evaluation parameters include appearance, surface characteristics, drug content, colour change, pH, particulate matter, assay, preservative content, pyrogenicity, and sterility[46].

Solubility studies

The solubility of a drug within the proliposomal formulation is crucial because it determines the drug's availability for absorption and subsequent therapeutic effect in the body, especially for poorly water-soluble candidates. It aids in selecting the dissolution media for in vitro studies, understanding drug ionization, and identifying the optimal site for release and absorption[47]. While many authors have discussed enhanced drug dissolution with proliposomes, only a few studies have addressed improved drug solubility within proliposomal formulations. In a specific report, Fei et al. highlighted the dynamic partition coefficient of the proliposomal formulation in an n-octanol/buffer system[48].

In vitro drug release:

In vitro drug release is a vital aspect of proliposomal formulation characterization. Often employed to enhance the solubility of poorly soluble drugs, proliposomes serve as drug delivery tools[40]. Understanding the dissolution profile in physiologically relevant media is crucial, offering insights into release behavior and potential in vivo effects. This knowledge becomes particularly important when translating proliposomal powders into diverse dosage forms like capsules or tablets[49]. Dissolution data aids in identifying optimal lipid

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and lipid composition for the selected drug. There are several methods available for conducting in vitro drug release studies for proliposomes, such as the USP dissolution apparatus Type I, Franz diffusion cell, dialysis tubing, reverse dialysis, cellophane dialyzing membrane, Keshary-Chien diffusion cell, and spectrapormolecular porous membrane tubing[42].Franzdiffusion cells can be used to test drug release in-vitro. Alternatively, a dialysis bag is preferred for studies involving hydrated liposomal dispersion, with drug release influenced by factors such as drug molecular weight, liposome size, agitation speed, release media, and dialysis bag molecular cut-off size[50].

APPLICATIONS

Proliposomes have been studied for diverse routes of administration, encompassing oral, transdermal, mucosal, nasal, ocular, pulmonary, and parenteral delivery.. Derived liposomes offer benefits as drug carriers, such as lower cost, reduced toxicity, convenient storage, handling, and enhanced stability.

Oral delivery

Although oral drug delivery remains the preferred route, liposomes face challenges in stability and unpredictable absorption. Proliposomes, as a free-flowing powder, pioneer the delivery of liposomes in solid forms like tablets or capsules, overcoming previous limitations. Moreover, liposomes form upon contact with biological fluids at the absorption site, ensuring the integrity of liposomes is retained. Domperidone, a 5HT3 receptor antagonist for nausea and vomiting, faces challenges like low aqueous solubility and significant gastric and hepatic firstpass metabolism after oral administration[43]. Chen B et al. explored Proliposomes for oral delivery of total biflavonoids extract from Selaginella doederleinii. They formulated liquid proliposomes, finding improved oral delivery of Selaginella doederleinii. Additionally, proliposomes demonstrated promise for the oral delivery of poorly soluble dehydrosilymarin[51]. Kunamaneni et al formulated aliskiren Hemifumarate Proliposomes for Improved Oral Drug Delivery which is a poorly bioavailable drug. [52].

Transdermal delivery:

Phospholipids, as the primary component in liposomal systems, seamlessly integrate with skin lipids, maintaining optimal hydration conditions to improve drug permeation. Upon application to mucosal membranes, proliposomes are expected to form liposomes upon contact with mucosal fluids. These resulting liposomes function as sustained-release dosage forms for loaded drugs, modulating diffusion across the skin. Various studies explore the feasibility of proliposomes as sustained transdermal dosage forms[53].

Mucosal delivery:

Proliposomes transform into vesicular structures (liposomes) within the body's aqueous environment on mucosal surfaces. The phospholipids within them naturally interact with biological membranes. The drug, dispersed within the bilayers, enhances its activity. This innovative approach overcomes challenges like stability and loading associated with traditional liposomal preparations[54].

Ophthalmic delivery:

Achieving optimal drug concentration in ocular drug delivery is challenging due to the eye's protective mechanisms. Developing a drug delivery system that reaches therapeutic levels requires a comprehensive understanding of the eye's static and dynamic barriers. Liposomes, being biodegradable nanocarriers, have been explored for ophthalmic drug delivery. They enhance permeation of poorly absorbed drugs by binding to the corneal surface and improving residence times[55].

Pulmonary delivery:

Proliposomes exhibit significant promise for delivering diverse pulmonary drugs. In a study conducted by Khan et al., the objective was to develop spray-dried proliposome (SDP) powder formulations as carrier particles to improve aerosolization efficiency for non-invasive drug delivery targeting pulmonary regions, with the goal of achieving both localized and systemic effects. The performance evaluation of these formulations was carried out utilizing a next-generation impactor (NGI) in conjunction with a dry powder inhaler[56].

Nasal delivery:

Nasal drug delivery has gained prominence as a convenient and reliable route for both local and systemic drug administration. Proliposomes demonstrate potential in nasal drug delivery, offering the combined advantages of fast onset (surface drug) and prolonged drug action (encapsulated drug)[57]. Duong VA et al found that when liposome-encapsulated drugs and genes are administered into the nasal cavity, their main route to the systemic circulation is through absorption in

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the respiratory region. Moreover, they have the capability to directly access the brain via the olfactory pathway. Liposomes play several crucial roles in this process: safeguarding drugs and genes from enzymatic degradation, improving drug absorption across the nasal epithelium, and extending their duration in the nasal cavity. Additionally, intranasal liposomes show potential for vaccine delivery by serving as a platform for loading antigens and acting as vaccine adjuvants to stimulate a robust immune response[58].

II. CONCLUSION

Pro-liposomes emerge as apromising drug carrier for the future, addressing stability, bioavailability, and solubility challenges associated with poorly soluble drugs. They offer noninvasive drug delivery into or across the skin, serving as a superior alternative to traditional liposomal systems due to enhanced physical and chemical stability. Their dry powder form makes them suitable for various unit dosage forms like tablets, capsules, and beads, facilitating broad pharmaceutical applications. Pro-liposomes are utilized orally, parenterally, topically, and in cosmetic and hair technologies, sustained release formulations, diagnostics, and gene delivery. They play a pivotal role in diverse delivery systems, yet further research is needed to explore their potential in nutraceuticals, herbal actives, and synthetic formulations, urging the development of scalable batches for both drug and natural preparations.

REFERENCE

[1]. Gupta M, Chaurasia A, Chaurasiya A.Proliposomes as Pharmaceutical Drug Delivery System. International Journal of Pharmaceutical Research and Applications. 2023;8(1):1102-1108.

[2]. kumari P, Maurya MP, Mishra JN. Formulation and Evaluation of Liposomal Gel with Dapsone. Journal of Population Therapeutics and Clinical Pharmacology. 2023;30(4):777-790.

[3]. Singh N, Kushwaha P, Ahmad U, Abdullah M, Proliposomes: An approach for the development of stable liposome. Ars Pharm. 2019;60(4):231-240.

[4]. Shah N, Patel K. Formulation, Development and Characterization of Liposome-based Gel of Eberconazole Nitrate for Topical Delivery. International Journal of Pharmaceutical Investigation. 2023;13(3):485-495.

[5]. Dutta A, Borah C. Proliposomal Drug Delivery System: An Updated Review. IJTSRD. 2023;7(4):318-327.

[6]. Muneer S, Masood Z, Butt S, Anjum S, Zainab H, Anwar N, Ahmad N. Proliposomes as Pharmaceutical Drug Delivery System: A Brief Review. J Nanomed Nanotechnol 2017;8(3):448.

[7]. Akram N, Afzaal M, Saeed F, Shah YA, Faisal Z, Asghar A, Ateeq H, Nayik GA, Wani SH, Hussain M, Asif Shah M. Liposomes: a promising delivery system for active ingredients in food and nutrition. International Journal of Food Properties.2023;26(1):2476-2492.

[8]. Nsairat H, Khater D, Sayed U, Odeh F, Al Bawab A, Alshaer W. Liposomes: Structure, composition, types, and clinical applications. Heliyon. 2022;8(5): 9394-9399.

[9]. Dhiman N, Sarvaiya J, Mohindroo P. A drift on liposomes to proliposomes: Recent advances and promising approaches. Journal of Liposome Research. 2022;32(4):317-331.

[10]. Rahul J, Mukund T, Kalyani F, Monali M, Shrikant K. Formulation and Evaluation of Ketoconazole Proliposomal Gels. Int. J. Pharm. Sci. Rev. Res. 2022;77(1):220-225.

[11]. Sherpa LS, Kumar I, Chaudhary A, Lepcha B. Liposomal drug delivery system: Method of preparations and applications. Journal of Pharmaceutical Sciences and Research. 2020;12(9):1192-1197.

[12]. Lombardo D, Kiselev MA. Methods of liposomes preparation: Formation and control factors of versatile nanocarriers for biomedical and nanomedicine application. Pharmaceutics. 2022;14(3):543-552.

[13]. Matsuura-Sawada Y, Maeki M, Uno S, Wada K, Tokeshi M. Controlling lamellarity and physicochemical properties of liposomes prepared using a microfluidic device. Biomaterials science. 2023;11(7):2419-2426.

[14]. Pande S. Liposomes for drug delivery: review of vesicular composition, factors affecting drug release and drug loading in liposomes. Artificial Cells, Nanomedicine, and Biotechnology. 2023;51(1):428-40.

[15]. Nambiar NR, Gaur S, Ramachandran G, Pandey RS, Nath LR, Dutta T, Sudheesh MS. Remote loading in liposome: a

review of current strategies and recent developments. Journal of Liposome Research. 2024; 10:1-3.

[16]. Pauli G, Tang WL, Li SD. Development and characterization of the solvent-assisted active loading technology (SALT) for liposomal loading of poorly water-soluble compounds. Pharmaceutics. 2019;11(9):465-471.

[17]. Swain B, Koilpillai J, Narayanasamy D. Systematic Review on Recent Advancements and Liposomal Technologies to Develop Stable Liposome. Current Trends in Biotechnology and Pharmacy. 2023;17(1):735-748.

[18]. Kulkarni S, Betageri G, Singh M. Factors affecting microencapsulation of drugs in liposomes. J Microencapsul. 1995;12(3):229-246.

[19]. Jeon D, Kim KT, Baek MJ, Kim DH, Lee JY, Kim DD. Preparation and evaluation of celecoxib-loaded proliposomes with high lipid content. European journal of pharmaceutics and biopharmaceutics. 2019;141:139-148.

[20]. Byeon JC, Lee SE, Kim TH, Ahn JB, Kim DH, Choi JS, Park JS. Design of novel proliposome formulation for antioxidant peptide, glutathione with enhanced oral bioavailability and stability. Drug delivery. 2019;26(1):216-225.

[21]. Bi Y, Lv B, Li L, Lee RJ, Xie J, Qiu Z, Teng L. A liposomal formulation for improving solubility and oral bioavailability of nifedipine. Molecules. 2020;25(2):338-347.

[22]. Patel P, Garala K, Singh S, Prajapati BG, Chittasupho C. Lipid-Based Nanoparticles in Delivering Bioactive Compounds for Improving Therapeutic Efficacy. Pharmaceuticals. 2024;17(3):329-336.

[23]. Nakhaei P, Margiana R, Bokov DO, Abdelbasset WK, Jadidi Kouhbanani MA, Varma RS, Marofi F, Jarahian M, Beheshtkhoo N. Liposomes: structure, biomedical applications, and stability parameters with emphasis on cholesterol. Frontiers in bioengineering and biotechnology. 2021;9:1-23.

[24]. Chordiya D, Shilpi S, Choudhary D, Saraogi GK, Sharma M, Kalyane D, Tekade RK. Proliposomes: a potential colloidal carrier for drug delivery applications. InThe future of pharmaceutical product development and research 2020;1, 581-608.

[25]. Patel HG, Jain SK, Nigam V. Review of Proliposomal Gel for Transdermal drug delivery system. World Journal of Biology Pharmacy and Health Sciences. 2023;14(3):332-40.

[26]. Jeon D, Kim KT, Baek MJ, Kim DH, Lee JY, Kim DD. Preparation and evaluation of celecoxib-loaded proliposomes with high lipid content. European journal of pharmaceutics and biopharmaceutics. 2019;141:139-48.

[27]. Amalia E, Sopyan I, Putriana NA, Sriwidodo S. Preparation and molecular interaction of organic solvent-free piperine pro-liposome from soy lecithin. Heliyon. 2023;9(6):166-174.

[28]. Lee MK. Liposomes for enhanced bioavailability of water-insoluble drugs: In vivo evidence and recent approaches. Pharmaceutics.2020;12(3):1-30.

[29]. Adel IM, Elmeligy MF, Abdelrahim ME, Maged A, Abdelkhalek AA, Abdelmoteleb AM, Elkasabgy NA. Design and characterization of spray-dried proliposomes for the pulmonary delivery of curcumin. International journal of nanomedicine. 2021;16:2667-2687.

[30]. Khan I, Al-Hasani A, Khan MH, Khan AN, -Alam FE, Sadozai SK, Elhissi A, Khan J, Yousaf S. Impact of dispersion media and carrier type on spray-dried proliposome powder formulations loaded with Beclomethasone dipropionate for their pulmonary drug delivery via a next generation impactor. Plos one. 2023;18(3):281-298.

[31]. Franco P, De Marco I. Supercritical antisolvent process for pharmaceutical applications: A review. Processes. 2020;8(8):938-968.

[32]. Jia J, Zhang K, Zhou X, Ma J, Liu X, Xiang A, Ge F. Berberine-loaded solid proliposomes prepared using solution enhanced dispersion by supercritical CO2: Sustained release and bioavailability enhancement. Journal of drug delivery science and technology. 2019;51:356-363.

[33]. Murakami T, Bodor E, Bodor N. Factors and dosage formulations affecting the solubility and bioavailability of P-glycoprotein substrate drugs. Expert Opinion on Drug Metabolism & Toxicology. 2021;17(5):555-580.

[34]. Shaik NB, Lakshmi PK, VV BR. Proliposome: A Novel Solution for the Stability of Liposomes-A Review. IJPSN. 2022;15(3):65-79.
[35]. Singh P, Bodycomb J, Travers B, Tatarkiewicz K, Travers S, Matyas GR, Beck Z. Particle size analyses of polydisperse liposome formulations with a novel multispectral advanced nanoparticle tracking technology. International journal of pharmaceutics. 2019;6:566-680.
[36]. Shaik NB, Shakelli D, Lakshmi PK, Basavarao VV. Formulation and Evaluation of Dolutegravir Proliposomal Powder for Pediatric HIV Patients. International Journal of Pharmaceutical Investigation. 2020;10(4):471-478.
[37]. Janga KY, Jukanti R, Velpula A, Sunkavalli S, Bandari S, Kandadi P, Veerareddy PR. Bioavailability enhancement of zaleplon via proliposomes: Role of surface charge. European journal of pharmaceutics and biopharmaceutics. 2012;80(2):347-357.
[38]. Qu F, Sun Y, Bi D, Peng S, Li M, Liu H, Zhang L, Tao J, Liu Y, Zhu J. Regulating size and charge of liposomes in microneedles to enhance intracellular drug delivery efficiency in skin for psoriasis therapy. Advanced Healthcare Materials. 2023;12(31):2301-2314.
[39]. Fu DW, Xu H, Sun RQ, Liu XL, Ji Z, Zhou DY, Song L. Engineering Marine Phospholipid Nanoliposomes via Glycerol-Infused Proliposomes: Mechanisms, Strategies, and Versatile Applications in Scalable Food-Grade Nanoliposome Production. Food Chemistry. 2024:448;139-150.
[40]. Nagarsheth A, Patel D, Thakkar H. Formulation and evaluation of proliposomal tablet of Diclofenac sodium. Journal of Drug Delivery Science and Technology. 2022;71:103-153.
[41]. Moghimipour E, Gorji A, Yaghoobi R, Salimi A, Latifi M, Aghakouchakzadeh M, Handali S. Clinical evaluation of liposome-based gel formulation containing glycolic acid for the treatment of photodamaged skin. Journal of Drug Targeting. 2024 ;32(1):74-79.
[42]. Shah H, Madni A, Rahim MA, Jan N, Khan A, Khan S, Jabar A, Ali A. Fabrication, in vitro and ex vivo evaluation of proliposomes and liposomal derived gel for enhanced solubility and permeability of diacerein. Plos one. 2021;16(10):258-271.
[43]. Swarnalatha N, Maravajhala V. Formulation, in vitro, and in vivo evaluation of taste-masked oral disintegrating tablets of fexofenadine hydrochloride using semisynthetic and natural superdisintegrants. International Journal of Applied Pharmaceutics. 2021:13(5);99-108.
[44]. Lodh H, Sheeba FR. Formulation and Evaluation of Nifedipine Bilayer Floating Tablets. Asian Journal of Pharmaceutical Research. 2023;13(4):1-45.
[45]. Jyothi VG, Bulusu R, Rao BV, Pranothi M, Banda S, Bolla PK, Kommineni N. Stability characterization for pharmaceutical liposome product development with focus on regulatory considerations: An update. International Journal of Pharmaceutics. 2022;624:122-132.
[46]. Mohite P, Singh S, Pawar A, Sangale A, Prajapati BG. Lipid-based oral formulation in capsules to improve the delivery of poorly water-soluble drugs. Frontiers in Drug Delivery. 2023;3:123-132.
[47]. Bao Z, Yung F, Hickman RJ, Aspuru-Guzik A, Bannigan P, Allen C. Data-driven development of an oral lipid-based nanoparticle formulation of a hydrophobic drug. Drug Delivery and Translational Research. 2023:1;1-6.
[48]. Mohanty S, Sahoo AK, Konkimalla VB, Pal A, Si SC. Naringin in combination with isothiocyanates as liposomal formulations potentiates the anti-inflammatory activity in different acute and chronic animal models of rheumatoid arthritis. ACS omega. 2020;5(43):28319-28332.
[49]. Abhishek K, Neha, Sakshi T. Formulation and evaluation of Liposomal Gel for the Treatment of Acne. International Journal of Pharmacy and Pharmaceutical Research.2023;27(2):541-558.
[50]. Suryam G and Prasanna. Formulation and evaluation of Naproxen Proliposomal Gels. World Journal of Pharmacy and Pharmaceutical Sciences. 2019;8(11):331-340.
[51]. Chen B, Wang X, Lin D, Xu D, Li S, Huang J, Weng S, Lin Z, Zheng Y, Yao H,

Lin X. Proliposomes for oral delivery of total biflavonoids extract from Selaginella doederleinii: formulation development, optimization, and in vitro–in vivo characterization. International Journal of Nanomedicine. 2019:14;6691-6706.

[52]. Kunamaneni P, Kovvasu S, Yeung S, Wang J, Shah S, Betageri G. Aliskiren Hemifumarate Proliposomes for Improved Oral Drug Delivery: Formulation Development, In Vitro and In Vivo Permeability Testing. Molecules. 2022;27(15):4828-4839.

[53]. Kuznetsova DA, Vasilieva EA, Kuznetsov DM, Lenina OA, Filippov SK, Petrov KA, Zakharova LY, Sinyashin OG. Enhancement of the transdermal delivery of nonsteroidal anti-inflammatory drugs using liposomes containing cationic surfactants. ACS omega. 2022 Jul 1;7(29):25741-25750.

[54]. Jawadi Z, Yang C, Haidar ZS, Santa Maria PL, Massa S. Bio-Inspired Muco-adhesive polymers for drug delivery applications. Polymers. 2022;14(24):54-59.

[55]. Yasser M, El Naggar EE, Elfar N, Teaima MH, El-Nabarawi MA, Elhabal SF. Formulation, optimization and evaluation of ocular gel containing nebivolol Hcl-loaded ultradeformable spanlastics nanovesicles: In vitro and in vivo studies. International Journal of Pharmaceutics: X. 2024;7:228-241.

[56]. Khan I, Al-Hasani A, Khan MH, Khan AN, -Alam FE, Sadozai SK, Elhissi A, Khan J, Yousaf S. Impact of dispersion media and carrier type on spray-dried proliposome powder formulations loaded with beclomethasone dipropionate for their pulmonary drug delivery via a next generation impactor. Plos one. 2023;18(3):281860-281872.

[57]. Khute S, Jangde RK. Optimization of Nasal Liposome Formulation of Venlafaxine Hydrochloride using a Box-Behnken Experimental Design. Current Therapeutic Research. 2023;99:100714-100729.

[58]. Duong VA, Nguyen TT, Maeng HJ. Recent advances in intranasal liposomes for drug, gene, and vaccine delivery. Pharmaceutics. 2023;15(1):207-215.