International Journal of Trend in Scientific Research and Development (IJTSRD)
Volume 7 Issue 4, July-August 2023 Available Online: www.ijtsrd.com e-ISSN: 2456 – 6470

Proliposomal Drug Delivery System: An Updated Review

Ankit Dutta, Chandramita Borah

Department of Pharmaceutics, Giirijananda Chowdhury Institute of Pharmaceutical Science, Azara, Guwahati, Assam, India

ABSTRACT

A bilayer of phospholipids makes up the tiny vesicles known as liposomes, which are a revolutionary drug delivery system that releases drugs at a predefined pace controlled by factors such as need, pharmacological characteristics, drug profile, physiological state of the body, etc. However, liposomes have poor stability issues, which makes storage a challenge. To get around this issue In 1986, pro-liposomes (PLs) were found. Granular pro-liposomes flow freely. Drug and phospholipid precursor compounds that, when hydrated, form liposomes. This essay evaluates numerous characteristics of pro-liposomes, their manufacturing process, analysis, uses, and highlighting their potential to be used for many administration methods.

How to cite this paper: Ankit Dutta | Chandramita Borah "Proliposomal Drug Delivery System: An Updated Review" Published in International Journal of Trend in Scientific Research and Development (ijtsrd), ISSN: 2456-6470, Volume-7 | Issue-4, August 2023, pp.318-327, URL: www.ijtsrd.com/papers/ijtsrd59692.pdf

IJTSRD59692

INTRODUCTION

Dr. Alec D. Bangham, a British haematologist, originally described liposomes in 1961 at the Babraham Institute in Cambridge. Greek terms "Lipos" (fat) and "Soma" (body) are the origin of the word "liposome"[1]. Liposomes are the most widely used, well-researched, and efficient new drug delivery method[2]. The term "liposome" refers to a tiny, spherical vesicle with an aqueous inside encased in phospholipid molecules. Drug compounds may be integrated into the lipid bilayer or the aqueous phase. They are frequently employed as a means of delivering nutrients and pharmaceutical medications in order to lessen their negative effects and increase the stability and efficacy of the drug[3]. Before reaching the intended place to exert therapeutic activity, Liposomes must be stable and undamaged both during the storage period and before being released onto the market. Liposomes are relatively unstable colloidal structures, nonetheless, because of their physical and chemical instability[4].

In order to address the stability problem with liposomes, a novel "pro-liposome" approach has been devised that can swiftly create liposomes on demand and with minimal modification[5]. Liposomal suspension may have a short shelf life. In 1986, pro-liposomes (PLs) were found[6]. Pro-liposomes are granular, dry items that flow freely when they come into touch with biological fluids in the body or when they are moistened. They are made up of phospholipid and porous powder that is water soluble[7].

Pro-liposome is one of the most popular and economical processes for creating commercial liposome products. They are accessible in dry powder form, which makes them simple to distribute, move, measure, and store. This makes the system versatile. Before being administered, liposomes can either be created in vitro using an appropriate hydration fluid or in vivo under the effect of biological fluids in the body[8]. Creating pro-liposomal formulations can solve many medications' solubility and bioavailability issues[9].

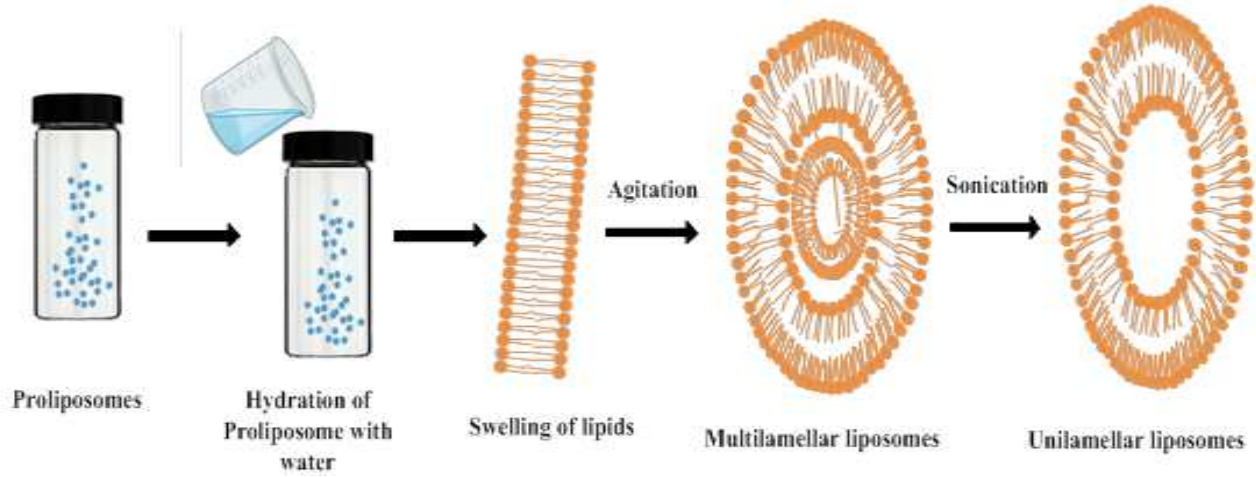

Fig 1: Mechanism of formation of liposomes from proliposomes

Structure and the main components of Proliposome:

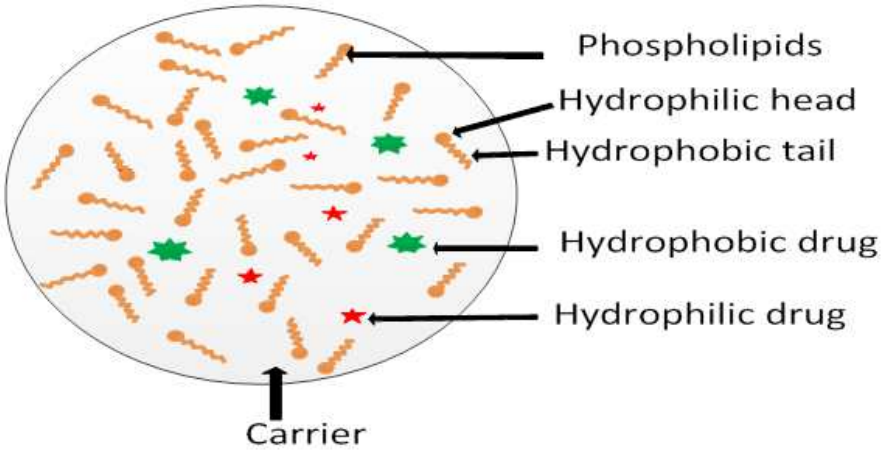

Fig 2: Structure of Proliposome

Formulation components of proliposomes[10,11,12,13]

Various formulation components used in the preparation of proliposomes with their characteristics is given in table 1.

Formulation component	Examples	Reasons
Phospholipids	Phosphotidylcholine(lecithin) Phosphatidyl ethanolamine Phosphatidyl glycerol Phosphatidyl serine	Main body of the proliposome
Steroids	Cholesterol	Provide stability to the proliposome
Carrier	Lactose monohydrate(LMH), Mannitol, Sorbitol, Microcrystalline Cellulose(MCC)	Rapid conversion of liposomal dispersion on hydration. Forms free flowing dry products.
Solvents	Ethanol, Methanol, Chloroform, Ether	Provide softness to vesicle membrane.

Table 1: Formulation components of proliposomes

Phospholipids

The creation of proliposomes can be done using a variety of lipids. The most often utilised phospholipids are phosphatidylcholines (PC). Lecithin, another name for PCs, may be derived from both natural and artificial sources. When compared to micellar structures, they form bilayer sheets, which is different from other amphipathic molecules. Egg yolk, soy beans, and very seldom the heart and spinal cord of cattle, are the most often used natural PC sources. Due to their generally inexpensive cost, absence of net charge, and chemical inertness, they are frequently utilised as the main component in proliposomes. Sphingomyelin (SM), in addition to PC, is a component of neutral lipid bilayers. Oleic, lauryl, myristic, and other fatty acid chains are joined with polar head groups such as phosphatidylglycerol (PG), phosphatidylethanolamine (PE), phosphatidic acid (PA), and phosphatidylserine (PS), among others. Variety of phospholipids are provided by palmitic and stearic acid

structures. Despite the large range of phospholipids that are available, the synthesis of proliposomes is frequently restricted to the PCs and PGs families, mostly due to toxicological Purity, stability, and cost.

Steroids

Liposomal membrane frequently includes cholesterol and its derivatives as a component. Three impacts of their incorporation in liposomal membranes are known. improving the membrane's fluidity or micro viscosity, decreasing its permeability to water-soluble compounds, and stabilising it when in contact with biological fluids like plasma. It significantly alters the characteristics of phospholipid bilayers after inclusion. Although cholesterol does not naturally form bilayers, it may be incorporated at large amounts into phospholipid membranes. By making the bilayers more rigid and decreasing permeability, it enhances the retention of hydrophilic pharmaceuticals; however, for hydrophobic medications, it only enhances encapsulation when the drug input is below the liposome's encapsulation capacity.

Water soluble carriers

In order to conveniently modify the quantity of carrier needed to support the lipids, the carriers selected should have high surface area and porosity. Additionally, it permits a high surfactant to carrier mass ratio while proliposomes are being prepared.

Due to their water solubility, they enable the hydration-induced quick conversion of liposomal dispersion, and by carefully regulating the size of the porous powder, a very small range of reconstituted liposomes may be produced. Maltodextrin, mannitol, sorbitol, microcrystalline cellulose, magnesium aluminium silicates, and others are some of the carriers used.

Solvents

They are employed to provide the vesicle membrane suppleness. Ethanol, methanol, ether, and chloroform are the most frequently utilised volatile organic solvents.

Proliposomes Manufacturing Process:

Film Deposition on Carrier Method[10,14,15,16, 17,18]

This is the method using which Payne (in 1986) prepared proliposomes for the first time. Instrument used for proliposome preparation by this method is Rotary Evaporator which is attached with a vacuum and a water bath. The preparation of proliposomes by this method is described as a flowchart in the figure 3.

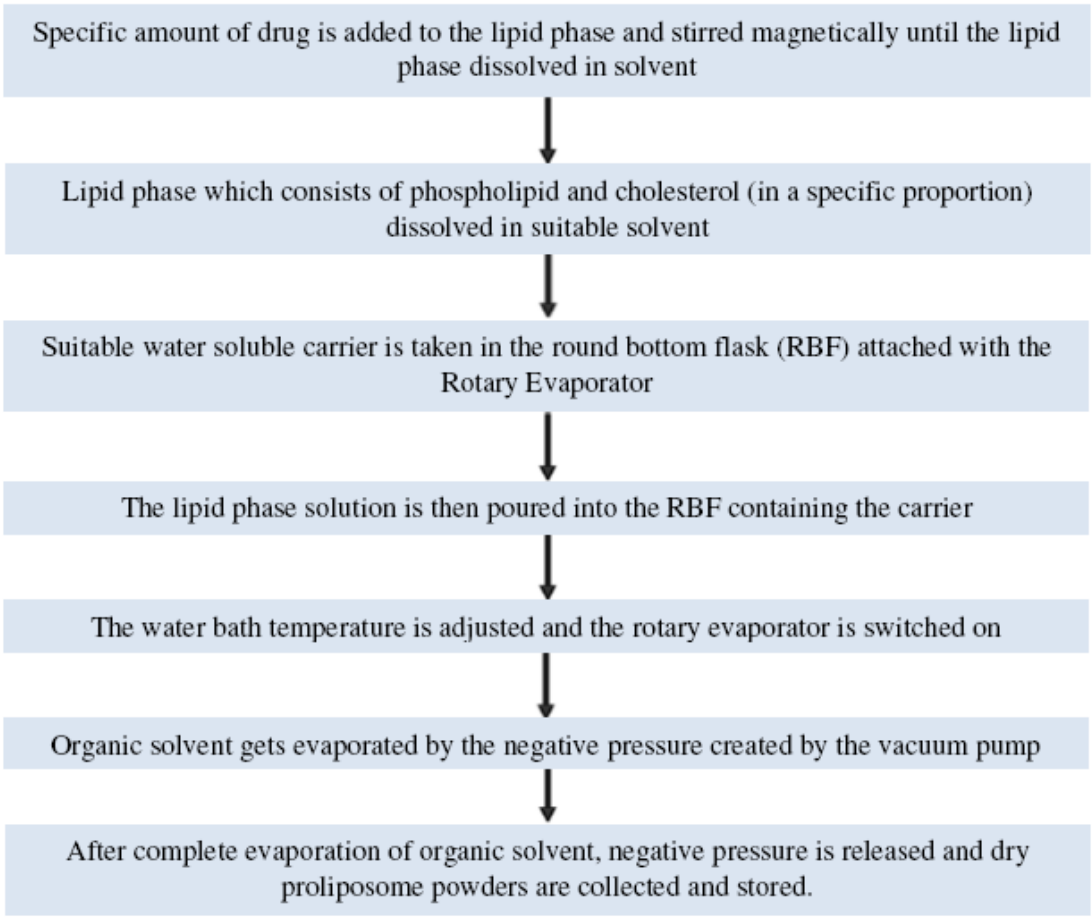

Fig 3: Flowchart for film deposition on carrier method for proliposome preparation

Spray Drying Method[12,19,20,21]

When proliposome particles of uniform shape and size is required, the spray drying method is the best method of proliposome preparation. This method is considered as the most suitable method for large scale proliposome production. Fig 4 depicts the flowchart of proliposome preparation by the process of spray drying.

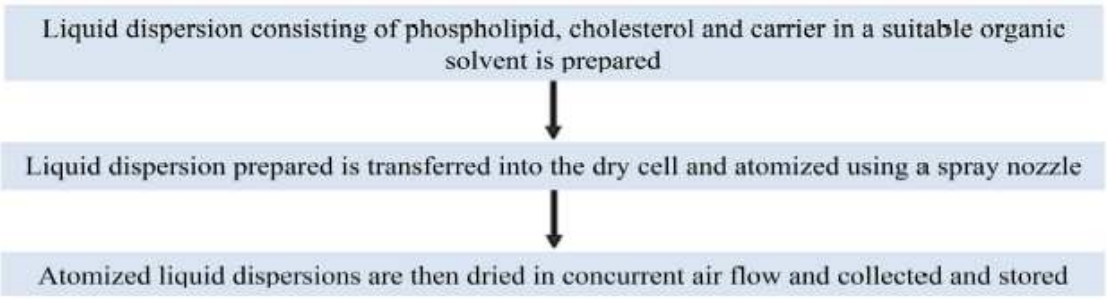

Fig 4: Flowchart of proliposome preparation by the process of spray drying

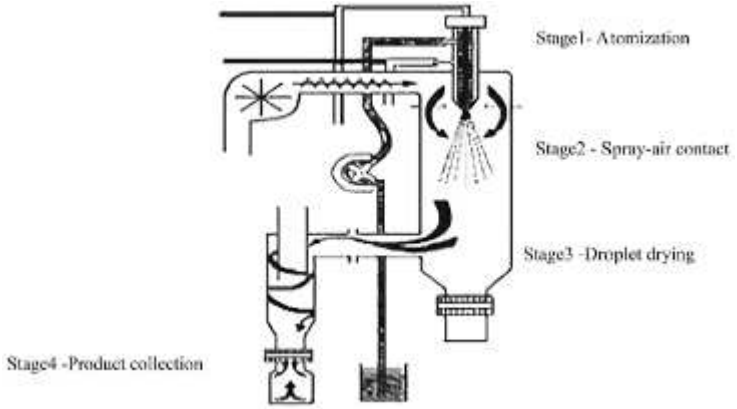

Fig 5: Schematic representation of spray drying method[10].

Super Critical Anti Solvent Method[10,13,22,23,24]

In this method, Supercritical Carbon Dioxide ($SCCO_2$) is used. This method is associated with some advantages like the steps of this method are simplest, mild operation temperature is required etc. Fig 6 depicts the flowchart of proliposome preparation by the process of spray drying. Various parts of the apparatus used in Super Critical Anti-Solvent Method is described in fig 7.

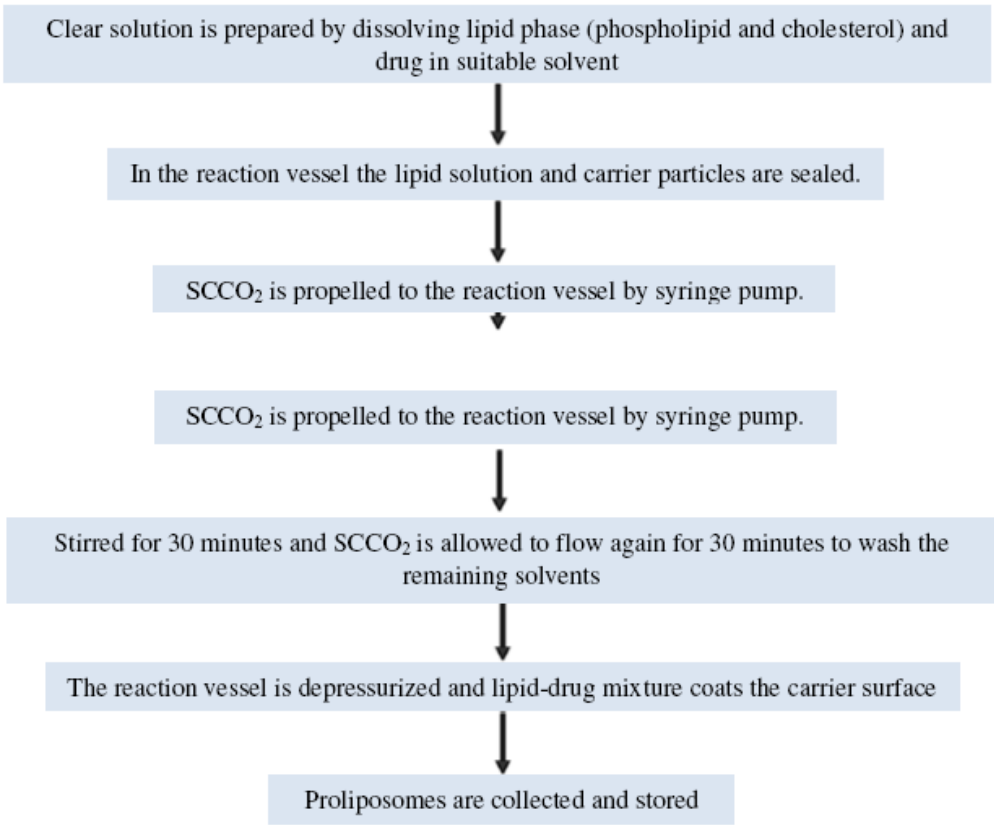

Fig 6: Flowchart of proliposome preparation by the process of Super Critical Anti-Solvent Method

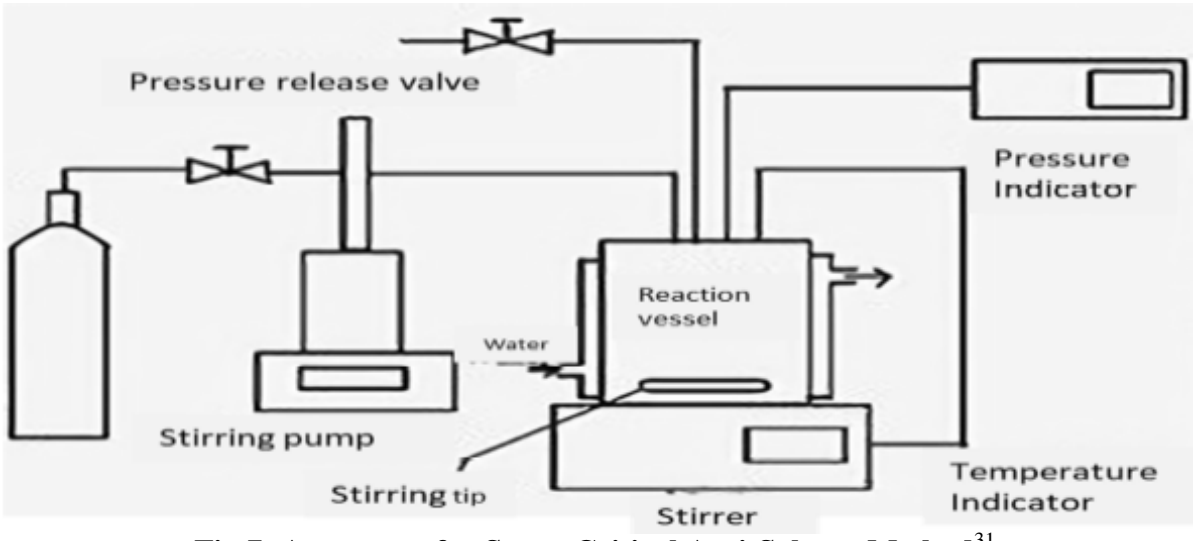

Fig 7: Apparatus for Super Critical Anti-Solvent Method[31]

Fluidized bed method[10,22,25]

Principle lying behind this method is particle coating. Fig 8 depicts the flowchart of proliposome preparation by the process of fluidized bed method. Various parts of the apparatus used in this method is described in fig 9.

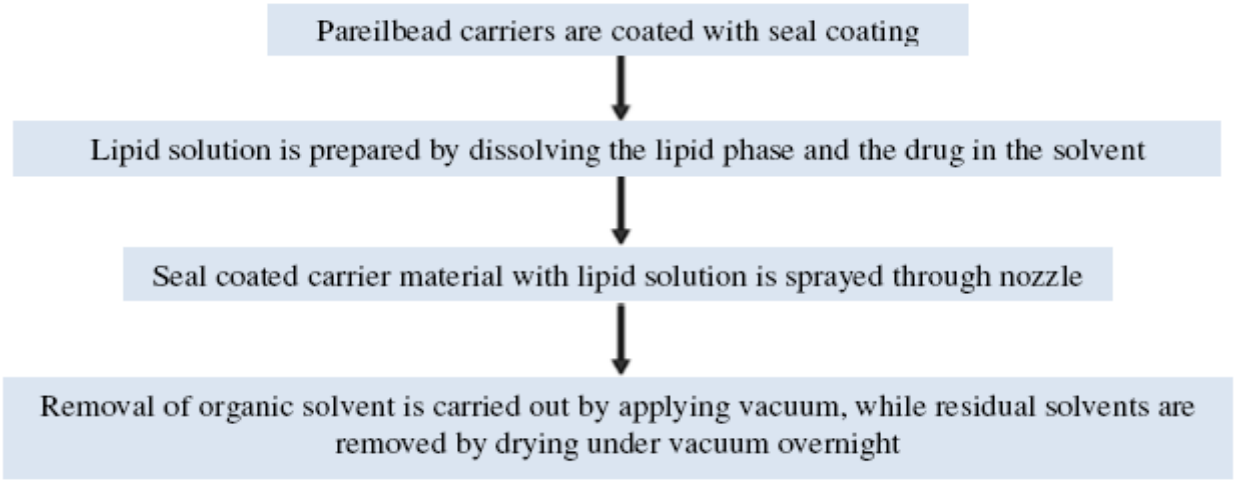

Fig 8: Flowchart of proliposome preparation by the process of Fluidized bed method

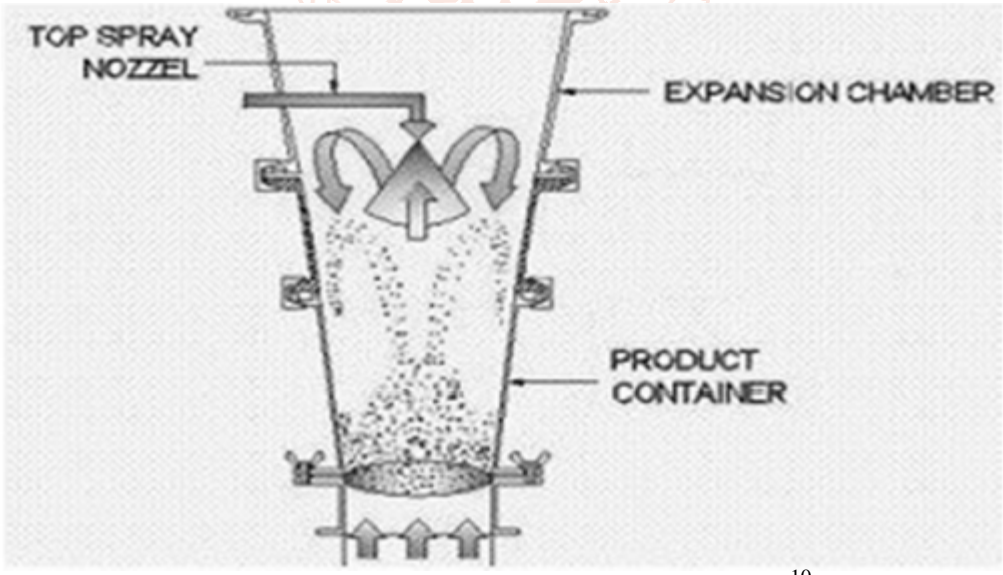

Fig 9: Apparatus for Fluidized Bed Method[10]

Some of the research work carried on proliposome as a drug carrier:

Table 2: Various research works on proliposomes with their references

Sl. no.	Preparation method	Drug	Indication	Route of administration	References
1.	Film Deposition on Carrier Method	Domperidone	For enhanced oral delivery of Domperidone	Oral	26
2.	Spray Drying Method	Nimodipine	Proliposome based soft gel toenhance oral delivery	Oral	3
3.	Film Dispersion-Freeze Drying Method	Silymarin	To improve oral bioavailability	Oral	28
4.	Spray Drying Method	Nicotine	Proliposomal gel	Transdermal	29
5.	Film Deposition on Carrier Method	Metformin hydrochloride	Proliposomal gel for type-II diabetes mallitus	Transdermal	14
6.	Thin Film Hydration Method	Repaglinide	Proliposomal gel	Transdermal	31
7.	Thin Film Hydration Method	Prednisolone	Proliposomal gel for Rheumatoid Arthritis	Transdermal	32
8.	Thin Film Hydration Method	Piroxicam	Proliposomal gel for Rheumatoid Arthritis	Transdermal	33
9.	Film Deposition on Carrier Method	Clotrimazole	Proliposomes for Vaginal Candidasis.	Mucosal	34
10.	Super Critical Anti Solvent Method and Thin Film Hydration Method	Cyclosporine	Dry proliposomes were prepared and two preparation method was compared	Ophthalmic	15
11.	Spray Drying Method	Levofloxacin	Proliposomes in dry powder aerosol for tuberculosis	Pulmonary	36
12.	Spray Drying Method	Isoniazid	Proliposome powder for tuberculosis	Pulmonary	37
13.	Spray Drying Method	Nicotine	Proliposomes	Nasal	38
14.	Spray Drying Method	Propanolol HCl	Proliposomes	Nasal	39
15.	Fluidized Bed Drying	Ibuprofen	Proliposomes for enhanced anti-inflammatory activity of Ibuprofen	IV	8
16.	Film Deposition on Carrier Method	Amphotericin B	Proliposomes	IV	41
17.	Film Deposition on Carrier Method	Methotrexate	Proliposomes	IV	42
18.	Film Deposition on Carrier Method	Adriamycin	Proliposomes for solid tumors, acute leukemia and lymphoma	IV	42
19.	Slurry Method	Paclitaxel	Paclitaxel loaded proliposomes for lung cancer	Pulmonary	44

EVALUATION OF PROLIPOSOMES

Morphology, angle of repose, rate of hydration, penetration, and permeation investigations are used to characterise proliposomes.

Particle size

A crucial property of proliposomes is their particle size. Scanning electron microscopy (SEM) may be used to analyse the size distribution and surface morphology (smoothness, roundness, and aggregation formation) of particles. The inability to read the carrier material's picture during the creation of proliposome[45] is evidence that phospholipid has been deposited on it.

Hydration Study and Vesicle formation

Understanding the liposomal vesicle generation during in vitro hydration of the proliposomal

formulation is crucial. Optical microscopy can verify the vesicle generation caused by the specific process. The liposome suspension must be spread out onto a glass slide and allowed to dry at room temperature before being examined to see whether any vesicles[46,14] have formed.

Measurement of zeta potential

Zeta potential is a further property of proliposomes that is of great interest. It serves as a gauge for particle charge, with surface charge increasing linearly with zeta potential absolute value. The zeta potential makes sense as a measure of particle stability. A proliposomal formulation that is only physically stable due to electrostatic repulsion would have a minimum zeta potential of about 30 mV, and this stability aids in avoiding aggregation[48].

Scanning electron microscopy (SEM)

It is employed to examine the PL powder's surface structure. It contrasts the appearance of liposomes with pure carrier substance.

Proliposomes' formulation is confirmed by the carrier material in the formulation, which also validates the phospholipids' arrangement on the carrier[21].

Transmission electron microscopy (TEM)

This technique is also used to examine the liposome structure following PL powder hydration. In this procedure, the proliposome powder is hydrated with distilled water before being examined under a microscope to determine the lamellarity and morphologies[8,51,49].

Flow property

The flow feature of a powder formulation can be used to explain content homogeneity and handling processing operations. Analysing the pro-liposome's properties is important for a formulation based on solid powder. The metrics Angle of repose, Carr's Index, and Hausner's ratio can be used to evaluate it[51,52].

APPLICATION OF PROLIPOSOMES

The following channels of administration can make use of Proliposome-

- **Parenteral Delivery**

Sterilisation of liposomes is essential for their development for parenteral use. Steam sterilisation, -irradiation, aseptic production, and filtration sterilisation are common sterilisation methods used in the pharmaceutical sector. Liposomal formulations may not be suited for terminal sterilisation using steam at 121°C because the high temperature may damage the liposome architecture owing to lipid hydrolysis, resulting in physical destabilisation. Irradiation is also inappropriate for liposomal dispersions because it increases the peroxidation of unsaturated lipids and induces hydrolysis of saturated lipids. Aseptic production is not frequently utilised since it is expensive and requires complicated validation. Because of the structural complexity of these vesicles and the loss of lipids caused by their non-specific adsorption to filters, filtration sterilisation of the final product can be difficult[53,54].

- **Oral Delivery**

Although liposomes have had limited success delivering medications via the oral route, oral drug delivery is still the preferred method of administration[8,52]. This is because liposomes exhibit inconsistent and unpredictable absorption characteristics and there is no stable dosage form for oral administration. This is because they are unable to maintain their integrity at the absorption location. PL is the first instance of putting liposomes into a solid dosage form, such tablets or capsules, because it is a freely flowing powder. Additionally, liposomes are created at the site of absorption when they come into touch with biological fluids, preserving their integrity. One of the most promising vehicles is the use of PLs. for increasing the effectiveness of medicines that are poorly soluble. It creates many lamellae greater levels of hydration thanks to vesicles due to the assimilation of soluble medicines a greater amount of hydrophobic cells inside the lamellae with liposomes. Also possible is conversion. from a crystalline to an amorphous state in the drug. Multilamellar's greater particle size Hydration-induced liposome formation assures lymphatic transport and enhances the drug bioavailability after high-dose administration beyond metabolism Additionally, the phospholipid molecules which form the backbone of the bilayer structure help to enhance the solubility of drug molecule.

- **Pulmonary Delivery**

The production of liposomes from phospholipids, which are naturally occurring in the lungs and are a component of lung surfactant, gives them a major advantage as a pulmonary drug delivery method. Drug encapsulation in liposomes offers regulated absorption, resulting in localised respiratory tract drug activity, longer drug presence in circulation, and less systemic side effects.[52,55]. Three different types of devices are used to administer drugs via the pulmonary route, including

A. Pressurised metered dose Inhalers (pMDI)

As the name implies, it entails dissolving or suspending medications in liquid propellants.

Hydrofluroalkanes are a poor solvent for phospholipids, which limits their use as non-ozone depleting propellants instead of CFCs for liposome delivery. Because they may be suspended in these propellants and act as carriers for pulmonary

distribution of liposomes through pMDI[52], PLs aid in overcoming this restriction.

B. Dry Powder Inhalers (DPIs)

These release the medication as a fine powder into the patient's airstream when they are inhaled.

Liposome distribution by DPI has various benefits, including regulated delivery, enhanced potency, less toxicity, homogenous local drug deposition, patient compliance, stability, and high dosage carrying capacity. PLs are the ideal solution for administering liposomes by DPIs since they are accessible in dry powder form[53,54]. Spray dried liposome encapsulated Dapsone DPI was created by Chougule[48] et al. to allow for extended medication retention in the lungs and to prevent Pneumocystis carinii pneumonia. In vitro drug release that lasted up to 16 hours was noted.

C. Nebulizers

The easiest method for delivering liposomes to the human respiratory system is nebulization, although this method has issues with medication stability and liposome leakage. It has been recommended that dry powder formulations be used to address these problems. Although it is possible to create dry powder by lyophilization and jet milling, the pressures associated in these methods tend to harm liposomes. As a result, PLs offer a reliable substitute for liposome nebulization. Additionally, the rapid creation of an isotonic liposome formulation from PLs in situ appears to have benefits over previous formulation methods[52,56].

- **Transdermal delivery**

Because they make up the majority of the liposomal system, phospholipids may easily bind to the lipids in the skin and preserve the correct level of moisture to enhance medication absorption. When PLs are placed to mucosal membranes, it is anticipated that upon coming into contact with mucosal fluids, they will form liposomes. These liposomes will then function as a sustained release dosage form for loaded pharmaceuticals. The formation of liposomes after hydration gives them the power to control skin diffusion. They accomplish this by merging with the skin's surface and creating a gradient of the intercalated drug's concentration throughout the skin. They improve skin permeability in this way. Additionally, the vesicle intercalation into the skin's internal lipid layers causes fluidization and disorganisation of the normal skin structure, eliminating the stratum corneum's barrier function.[47,56]

CONCLUSION

The problems with liposome stability have been greatly improved because to PLs. It has also opened up additional applications for liposomes, particularly in the field of oral delivery. Using techniques like fluidized bed drying and spray drying, PLs can be made on a massive scale. They can also be administered using traditional formulations. As a result, PLs are very commercially valuable as a means of entering the market.

References

[1] Dua JS, Rana AC, Bhandari AK (2012) Liposome: methods of preparation and applications. Int J Pharm Stud Res 3: 14-20.

[2] Hiremath PS, Soppimath KS, Betageri GV (2009) Proliposomes of exemestane for improved oral delivery: formulation and in vitro evaluation using PAMPA, Caco-2 and rat intestine. Int J pharm 380: 96-104.

[3] Sun C, Wang J, Liu J, Qiu L, Zhang W, et al. (2013) Liquid proliposomes of nimodipine drug delivery system: preparation, characterization, and pharmacokinetics. Aaps Phar 14: 332-338.

[4] Yadav A, Murthy MS, Shete AS, Sakhare S (2011) Stability aspects of liposomes. Ind J Pha Edu 45: 402-413.

[5] Uchegbu LF (2000) Publisher: CRC Press, 93-96.

[6] Payne NI, Timmins P, Ambrose CV, Ward MD, Ridgway F (1986) Proliposomes: a novel solution to an old problem. J pha sc 75: 325-329.

[7] Manjula D, Shabaraya AR, Shyale S (2014) Topical Delivery of Fenoprofen Proliposomes: Preparation, Evaluation and In Vitro Release. Int J Pha Sc In 3: 06-12.

[8] Janga KY, Jukanti R, Velpula A, Sunkavalli S, Bandari S, et al. (2012) Bioavailability enhancement of zaleplon via proliposomes: Role of surface charge. Eur J Phar Bio 80: 347-357.

[9] Ashok K, Jukanti R (2012) Euro J Phar Bio, pp: 347-357.

[10] Singh N, Kushwaha P, Ahmad U, Abdullah M. Proliposomes: an approach for the development of stable liposome.

[11] 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): 1-5.

[12] Parmar G, Bala R, Seth N, Banerjee A. Proliposome: Novel drug delivery system. World J Pharm Res. 2015 Apr 28; 4(7): 679-92.

[13] Gupta V, Barupal AK, Ramteke S. Formulation development and in vitro characterization of proliposomes for topical delivery of aceclofenac. Indian journal of pharmaceutical sciences. 2008 Nov; 70(6): 768.

[14] Shruthi MV, Parthiban S, Senthilkumar GP, Tamizmani T. Evaluation of potential hypoglycemic activity of proliposomal gel containing Metformin hydrochloride. Asian J Res Biol Pharm Sci. 2014; 2(2): 77-88.

[15] Karn PR, Jin SE, Lee BJ, Sun BK, Kim MS, Sung JH, Hwang SJ. Preparation and evaluation of cyclosporin A-containing proliposomes: a comparison of the supercritical antisolvent process with the conventional film method. International journal of nanomedicine. 2014; 9: 5079

[16] Rojanarat W, Changsan N, Tawithong E, Pinsuwan S, Chan HK, Srichana T. Isoniazid proliposome powders for inhalation-preparation, characterization and cell culture studies. International journal of molecular sciences. 2011 Jul 7; 12(7): 4414-34.

[17] Xu H, He L, Nie S, Guan J, Zhang X, Yang X, Pan W. Optimized preparation of vinpocetine proliposomes by a novel method and in vivo evaluation of its pharmacokinetics in New Zealand rabbits. Journal of controlled release. 2009 Nov 16; 140(1): 61-8.

[18] Lo YL, Tsai JC, Kuo JH. Liposomes and disaccharides as carriers in spray-dried powder formulations of superoxide dismutase. Journal of controlled release. 2004 Feb 10; 94(2-3): 259-72.

[19] Manani H, Prajapati B, Patel R. Review of Preliposomes as novel drug delivery system. The Pharma Innovation. 2016 Mar 1; 4(3, Part B).

[20] Colonna C, Conti B, Genta I, Alpar OH. Non-viral dried powders for respiratory gene delivery prepared by cationic and chitosan loaded liposomes. International journal of pharmaceutics. 2008 Nov 19; 364(1): 108-18.

[21] Shaji J, Bhatia V. Proliposomes: a brief overview of novel delivery system. Int J Pharm Biosci. 2013; 4: 150-60.

[22] Xia F, Hu D, Jin H, Zhao Y, Liang J. Preparation of lutein proliposomes by supercritical anti-solvent technique. Food hydrocolloids. 2012 Mar 1; 26(2): 456-63.

[23] Fei XI, Heyang J, Yaping Z, Xinqiu G. Supercritical antisolvent-based technology for preparation of vitamin D3 proliposome and its characteristics. Chinese journal of chemical engineering. 2011 Dec 1; 19(6): 1039-46.

[24] Chen CM, Alli D. Use of fluidized bed in proliposome manufacturing. Journal of pharmaceutical sciences. 1987; 76(5).

[25] Nalla P, Bagam S, Eedara BB, Dhurke R. Formulation and evaluation of domperidone oral proliposomal powders. Int. J. Pharm. Technol. Res. 2015; 7: 108-18.

[26] Chu C, Tong SS, Xu Y, Wang L, Fu M, Ge YR, Yu JN, Xu XM. Proliposomes for oral delivery of dehydrosilymarin: preparation and evaluation in vitro and in vivo. Acta pharmacologicasinica. 2011 Jul; 32(7): 973-80.

[27] Jung BH, Chung BC, Chung SJ, Lee MH, Shim CK. Prolonged delivery of nicotine in rats via nasal administration of proliposomes. Journal of controlled release. 2000 May 3; 66(1): 73-9.

[28] Kumara BC, Parthiban S, Senthil Kumar GP, Tamiz Mani T. Formulation and evaluation of proliposomal gel containing repaglinide using mannitol as water soluble carrier. Imperial Journal of Interdisciplinary Research. 2016; 2(5): 1777-86.

[29] Kurakula M, Srinivas C, Kasturi N, Diwan PV. Formulation and evaluation of prednisolone proliposomal gel for effective topical pharmacotherapy. International Journal of Pharmaceutical Sciences and Drug Research. 2012; 4(1): 35.

[30] Kurakula M, Pasula, N. Piroxicam proliposomal gel -A novel approach for topical delivery. J Pharm Res 2012; 5 (3): 1755.

[31] Ning MY, Guo YZ, Pan HZ, Yu HM, Gu ZW. Preparation and evaluation of proliposomes containing clotrimazole. Chemical and pharmaceutical bulletin. 2005; 53(6): 620-4.

[32] Rojanarat W, Nakpheng T, Thawithong E, Yanyium N, Srichana T. Levofloxacin-proliposomes: opportunities for use in lung tuberculosis. Pharmaceutics. 2012 Aug 13; 4(3): 385-412.

[33] Jung BH, Chung SJ, Shim CK. Proliposomes as prolonged intranasal drug delivery systems. STP Pharma sciences. 2002; 12(1): 33-8.

[34] Shin BN, Chang KK, Shim K. Proliposomes as an intranasal dosage form for the sustained delivery of propranolol. Journal of Controlled Release 1995; 34(3): 203-210.

[35] Katare OP, Vyas SP, Dixit VK. Effervescent granule based proliposomes of ibuprofen. Journal of microencapsulation. 1990 Jan 1; 7(4): 455-62.

[36] Park JM, Ahn BN, Yoon EJ, Lee MG, Shim CK, Kim CK. The pharmacokinetics of methotrexate after intravenous administration of methotrexate-loaded proliposomes to rats. Biopharmaceutics & drug disposition. 1994 Jul; 15(5): 391-407.

[37] Lee HJ, Ahn BN, Yoon EJ, Paik WH, Shim CK, Lee MG. Pharmacokinetics and tissue distribution of adriamycin and adriamycinol after intravenous administration of adriamycin-loaded neutral pro liposomes to rats. International journal of pharmaceutics. 1995 Jul 6; 121(1): 1-0.

[38] Khan I, Lau K, Bnyan R, Houacine C, Roberts M, Isreb A, Elhissi A, Yousaf S. A facile and novel approach to manufacture paclitaxel-loaded proliposome tablet formulations of micro or nano vesicles for nebulization. Pharmaceutical research. 2020 Jun; 37(6): 1-9.

[39] Song KH, Chung SJ, Shim CK. Preparation and evaluation of proliposomes containing salmon calcitonin. Journal of Controlled Release 2002; 84: 27-37.

[40] Payne NI, Browning I, Hynes CA. Characterization of proliposomes. J. Pharm. Sci 1986; 75(4): 330-333.

[41] Leigh M. Supra Vail Vaginal Gel. In: Michael J. Rathbone, Jonathan Hadgraft, Michael S. Roberts (eds.), Modified-Release Drug Delivery Technology, Marcel Dekker, New York; 2003. p. 791-800.

[42] Yan-Yu X, Yun Mei S, Zhi-Peng C, Qi-Neng P (2006) Preparation of silymarin proliposome: a new way to increase oral bioavailability of silymarin in beagledogs. Inter Phar 319: 162-168.

[43] Janga KY, Jukanti R, Velpula A, Sunkavalli S, Bandari S, et al. (2012) Bioavailability enhancement of zaleplon via proliposomes: Role of surface charge. Euro J Phar Biop 80: 347-357.

[44] Patil SD, Burgess DJ. Liposomes: Design and Manufacturing. In: James Swarbrick(ed.), Injectable Dispersed Systems Formulation, Processing, and Performance, Taylor & Francis, Boca Raton, 2005, pp. 249-353.

[45] Vemuri S, Rhodes CT, Preparation and characterization of liposomes as therapeutic delivery systems: a review. Pharm Acta Helv., 70: 95-111, (1995).

[46] Song KH, Chung SJ, Shim CK, Preparation and evaluation of proliposomes containing salmon calcitonin. J. Control. Rel, 84: 27–37, (2002).

[47] Hwang BY, Jung BH, Chung SJ, Lee MH, Shim CK, In vitro skin permeation of nicotine from proliposomes. J. Control. Rel., 49: 177–184, (1997).

[48] Mohammed AR, Bramwell VW, Coombes AGA, Perrie Y, Lyophilisation and sterilisation of liposomal vaccines to produce stable and sterile products. Methods, 40: 30–38, (2006).

[49] Deshmukh DD, Ravis WR, Betageri GV, Improved delivery of cromolyn from oral proliposomal beads. Int J Pharm, 358: 128–136, (2008).

[50] Kumar R, Gupta RB, Betageri GV, Formulation, Characterization and In Vitro Release of Glyburide from Proliposomal Beads. Drug Delivery, 8(1): 25-27, (2001).

[51] Xu H, He L, Nie S, et al., Optimized preparation of vinpocetine proliposomes by a novel method and in vivo evaluation of its pharmacokinetics in New Zealand rabbits. J. Control. Rel., 16: 61–68, (2009).

[52] Brocks DR, Betageri GV, Enhanced oral absorption of halofantrine enantiomers after encapsulation in a proliposomal formulation. Journal of Pharmacy and Pharmacology, 54: 1049-1053, (2002).

[53] Taylor KMG, Elhissi AMA. Preparation of Liposomes for Pulmonary Delivery Using Messdical Nebulizers. In: Gregory Gregoriadis (ed.), Liposome Technology Liposome Preparation and Related Techniques, 3rd Edn, Vol I, Informa Healthcare, New York, 2007, pp. 67-84.

[54] Sweeney LG, Wang Z, Loebenberg R, Wong JP, Lange CF, Finlay WH, Spray- freeze-dried liposomal ciprofloxacin powder for inhaled aerosol drug delivery. Int J Pharm., 305: 180–185, (2005).

[55] Jukanti R, Sheela S, Bandari S, Veerareddy PR, Enhanced bioavailability of exemestane via proliposomes based transdermal delivery. J Pharm Sci, 100(8): 3208-3222, (2011).

[56] Gupta V, Barupal AK, Ramteke, Formulation Development and in vitro Characterization of Proliposomes for Topical Delivery of Aceclofenac. Ind. J. Pharm. Sc., 70(6): 768–775, (2008)