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LIPOSOMAL VESICULAR DELIVERY SYSTEM: AN INNOVATIVE NANO CARRIER

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ABSTRACT

In current era of drug delivey system, the pharmaceutics specialized personal/professional worked as a F & D. As the researcher for development of specific formulation that has nano absorption capacity and it should have nano carrier properties. This testimonal will looked for the various approaches to get Liposomal vesicular Drug Delivery system that makes possible F & D innovative discovery journey. The various approaches shows that each and every method has pros and cons in itself, also we`ll look to provide that which method is best for which situation also we provided a laboratory based technique for production of Liposomes, also we looked to provide a pictorial based diagram for Drug Loading process as it`s one of the crucial process during formulation of Liposomes.

KEYWORDS: DOPE (dioleolylphosphatidylethanolamine), Convectional, High-pressure extrusion, conceivable, activated macrophages

INTRODUCTION

Many people are interested in using liposomes as a vehicle for cutting-edge medication delivery.[1] Alec D. Bangham created liposomes for the first time in 1961 while researching phospholipids and blood coagulation in England.

Because each phospholipid molecule has one water-soluble end and one water-insoluble end, it was discovered that phospholipids and water united to create a spherical right away. Drugs that were soluble in water were entrapped within the hydrophobic end aggregation, while drugs that dissolved in fat were integrated into the phospholipid layer.

A liposome is a spherical vesicle that is used to transport genetic material or drugs into cells. Its membrane is made of phospholipid bilayers. Liposomes can consist of pure components such as DOPE (dioleolylphosphatidylethanolamine) or naturally-derived phospholipids with mixed lipid chains, such as egg phosphatidylethonalimine.

The liposome contents can be delivered when the lipid bilayer fuses with another bilayer, such as the cell membrane. Liposomes can be propelled past the lipid bilayer by dissolving them in a solution containing DNA or medication, which would not ordinarily be able to permeate through the membrane. The method of introducing liposomes-mediated DNA transfection into a host cell is known as lipofection. Liposomes can be made by sonicating phospholipids in water. Low shear rates are used to create multilamellar liposomes, which resemble onion layers. Continued high-shear sonication tends to result in smaller unilamellar liposome formation.

- **Mechanism of liposomal Delivery Action**

The following are some of the ways that liposomes function both inside and outside of the body:[3]

1. Liposome adheres to the membranes of cells and gives the impression of fusing with them, allowing their contents to be released into the cell.
2. On occasion, they are absorbed by the cell, and their phospholipids are integrated into the cell membrane, releasing the medication that has been imprisoned inside.

   When phagocyte cells are included, the liposomes are picked up, the phospholipid walls are acted upon by organelles known as lysosomes, and the active chemicals within the pharmaceutical are released.

- **Type of Liposomes**

Liposomes can be classified into two types based on their structures.

a) **Unilamellar liposomes**: A single phospholipid bilayer sphere encasing an aqueous solution is present in unilamellar vesicles.

b) **Multilamellar Liposomes**: The structure of multilamellar vesicles is onion-like. An array of concentric phospholipid spheres divided by water layers forms a multilamellar structure when many Unilamellar vesicles form one inside the other in decreasing size.[4]

Methods of Liposome Formulation and Drug Loading

The following is a list of several methods for making lipososmesas. A few of the key techniques have been described.

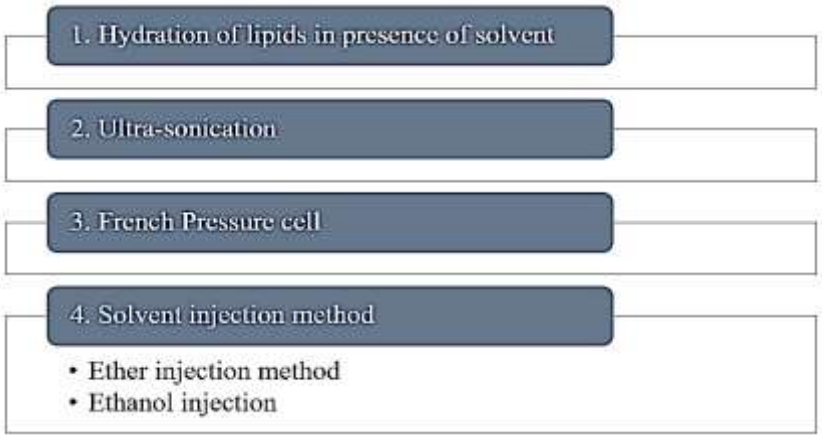

Figure No. 1: (A), Main Methods for Liposomes Preparation.

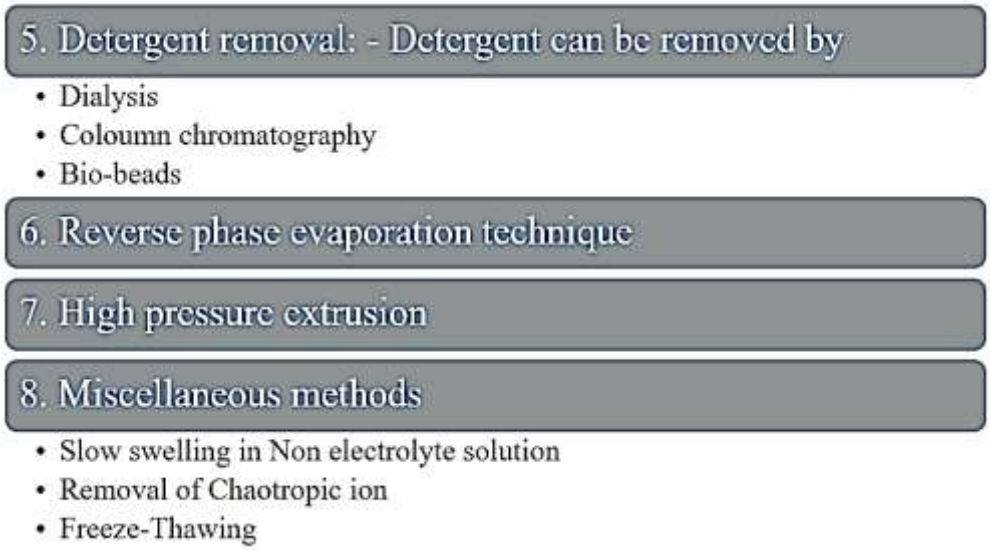

Figure No. 1: (B), Alternative Methods for Liposomes Preparation.

1. Handshaking Method

In order to produce liposome lipid molecules must be introduced into an aquatic setting. When dry lipid layer film is moistened the lamellae swell and grow into myelin figures. Only mechanical agitation provided by vortexing, shaking, swering or pippeting cause **myelin**

figures to break and reseal the exposed hydrophobic edges It is possible to create liposomes by shaking by hand.[6]

2. Convectional method

The process involves dissolving the phospholipids in an organic solvent (often a combination of chloroform and methanol) and using rotary evaporation under low pressure to deposit the solvents as a thin layer on the wall of the bottom flask. When an excess volume of aqueous buffer containing the medicine is introduced to the dried lipid film, MLVs develop on their own. those that contain liposomes can be distinguished from those that are not sequestered using gel filtering or liposome centrifugation. The amount of aqueous buffer (or drug solution) that will be trapped inside the interior compartments of the MLVs depends critically on the length of time given for hydration of the dry film and the agitation settings.[5]

3. Sonication technique[5]

This process, which is used to prepare SUVs, entails sonicating MLVs that were previously prepared by the standard method using a bath-type or probe-type sonicator in an inert atmosphere—typically nitrogen or argon. The idea behind sonication is to shake a suspension of MLVs by applying high frequency, pulsed sound waves, or "sonicenergy." SUVs with a diameter of between 15 and 50 nm are the result of this disruption of the MLVs. Therefore, the goal of sonication is to create a uniform dispersion of tiny vesicles that may be more capable of penetrating tissue. The bath and probe tip types of sonicators are the most widely utilized ones. The oxidation of unsaturated bonds in the phospholipids' fatty acid chains and hydrolysis into lyso phospholipids and free fatty acids are the main disadvantages of using sonication to prepare liposomes. The denaturation or inactivation of some thermolabile molecules (such as DNA, specific proteins, etc.) that are to be entrapped is another disadvantage.

4. High-pressure extrusion method[5]

Another approach to converting MLV suspensions to SUV ones is this one. By this strategy, suspensions of MLVs arranged by the convectional technique are more than once gone through channels polycarbonate layers with tiny pore distance across (0.8-1.0μm) under high tension up to 250 psi. By picking channels with proper pore sizes, liposomes of advantageous distances across can be delivered. The instrument of activity of the great tension expulsion strategy has all the earmarks of being similar as stripping an onion. As the MLVs are constrained through the little pores, progressive layers are stripped off until just a single

remaining parts. Other than decreasing the liposome size, the expulsion strategy produces liposomes of homogeneous size appropriations. A wide range of lipids can be utilized to shape stable liposomes by this strategy. Expulsion at low tensions <1 Mpa is conceivable when lipid focus is low, however the most regularly utilized pressures are around 5 Mpa. For better results, a new method makes use of 10.5 Mpa.

5. Solubilization and Detergent Removal Method[5]

This procedure, which is used to prepare LUVs, involves solubilizing the lipids with a detergent (surfactant). Non-ionic surfactants, such as n-octyl-bete-D-glucopyranose (octyl gluside), anionic surfactants, such as dodecyl sulphate, and cationic surfactants, such as hexadecyltrimethyl ammoniumbromide, are among the detergents used. The process entails dissolving the lipids in an aqueous solution containing the protein or proteins to be encapsulated and the detergent. To facilitate easy removal, the detergent should have a high critical micelle concentration (CMC). The detergent is then eliminated using column chromatography or dialysis. LUVs of a diameter of 0.08–0.2 μm are created after the detergent is removed. It has been discovered that this detergent removal technique is appropriate for encasing proteins with significant biological applications.

6. Reverse Phase Evaporation Technique

It comprises of a quick infusion of fluid arrangement of the medication into a natural dissolvable, which contains the lipid broke up with concurrent shower sonication of the blend prompting the development of water drops in the natural dissolvable (i.e., a "water-in-oil" emulsion). The subsequent emulsion is dried down to a semi strong gel in a rotational evaporator. The gel is then subjected to vigorous mechanical agitation to undergo a phase change from oil-in-oil dispersion (i.e., an aqueous suspension of the vesicles) to oil-in-oil dispersion. Some of the water droplets break apart during the agitation to form the external phase, while the rest form the entrapped aqueous volume. Largen unilamellar vesicles (measurement 0.1-1μm) are framed all the while. This strategy has been utilized to epitomize both little and macromolecules like RNA and different proteins without loss of movement. The normal impediment of this strategy is the openness of the material to be exemplified to natural solvents and mechanical unsettling, which can prompt the denaturation of certain proteins or breakage of DNA strands. Reports of such restrictions are anyway uncommon in the written works.

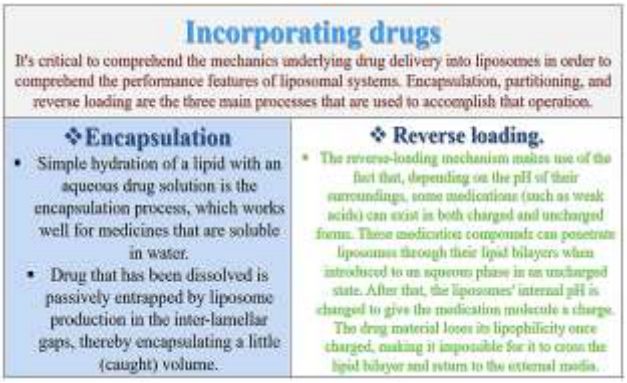

Figure No. 2: Methods for Incorporating Drugs in/during Liposomes Production.

Table No. 1: Application for Liposomes.

Sr. No.	Drug	Application	Commercial Name	Composition of Liposomes	Reference
1.	Ampicillin	Listeria monocytogenesis	-	CH/PC/PS	[14]
2.	Annamycin	Breast Cancer, Leukemia	Annamycin	Liposomes	[15]
3.	Amikacin	Bacterial Infection	MiKasome	HSPC/CH/DSPG	[12]
4.	Adriamycin	Stomach Cancer	-	DPPC/CH	[13]
5.	Amphotericin B	Systemic Fungal Infection	AmBisome	HSPC/CH/DSPG	[16]
6.	All-transretionic acid	Prostate Cancer, Leukemia	ATRAGEN	Liposomes	[17]
7.	Muramyl dipeptide	Immunostimulator	-	DSPC/PS 1:1	[18]
8.	Cyclosporin	Immunosuppresor	-	PC/CH	[21]
9.	Chloroquinine	Malaria	-	PC/PG/CH	[22]
10.	Doxorubicin	Cancer	Doxil	HSPC/CH/PEG	[23]
11.	Daunorubicin	Breast Cancer	Daunaxome	DSPC/CH	[24]
12.	Gangiciclovir	HSV	-	Liposomes	[25]
13.	Ciprofloxacin	Pseudomonas aerogonisa	-	DPPC	[19]
14.	Clodronate	Macrophage suppresion	-	PC/CH	[20]
15.	Intralukin-2	Immunostimulant	-	DMPC	[26]
16.	Mitoxantron	Colon Cancer	-	PC/CH	[27]
17.	Methorexate	Cancer	-	DPPC/PI	[28]
18.	Nystatin	Fungal Infection	Nyotran	Liposomes	[29]
19.	Prostaglandanin	Antiinflammatory	-	Liposomes	[32]
20.	Ribavirin	Herpes Simplex	-	PC	[33]
21.	Streptosotocin	Lymphocyte activator	-	DMPC/CH	[34]
22.	Pentostam	Leishmanioses	-	Niosomes	[30]
23.	Cisplastin	Mezotelioma	PLATAR	Liposomes	[31]
24.	Lurotecon	Cancer	NX211	Liposomes	
25.	Suramin	Trypanosomes	-	DPPC	[35]

1) Applications of liposomes in Medicine

The therapeutic and diagnostic uses of liposomes containing medications or different markers, as well as their use as a:-

a) model,
b) instrument, or
c) reagent

in the fundamental research of

a) cell interactions,
b) recognition processes, and the
c) mode of action of specific substances,

are the two main categories of liposome applications in pharmacology and medicine. Sadly, a lot of medications have a very **small therapeutic window**, which means that the therapeutic concentration and the hazardous concentration are not that far apart. Using the right drug carrier can alter the medication's temporal and geographical distribution alongside the human body, or its pharmacokinetics and biodistribution, and in many situations lessen toxicity or increase efficacy.[7]

Table No. 2: Application for Liposomes.

Sr. No.	Macrophage activation and vaccination
1.	Liposomes in parasitic diseases and infections
2.	Liposomes in anticancer therapy
3.	Liposomes in bioengineering
4.	Liposomes in cosmetics
5.	iposomes in agro-food industry

2) Macrophage Activation and Vaccination

There are a number of additional applications for the autophagic targeting of liposomes, such as immunization and macrophage activation. Certain naturally occurring poisons cause a potent macrophage response, which activates macrophages. Because small molecules with immunogenic qualities (haptens) cannot produce an immune response unless they are connected to a larger particle, this can be replicated and enhanced through the use of liposomes. Macrophage activation is triggered, for example, by liposomes containing muramyl tripeptide, the smallest immunogenic bacterial cell wall subunit. Larger and packed with more granulomas and lysosome material are activated macrophages.[8]

3) Liposomes in Parasitic Diseases and Infections

Conventional liposomes are perfect for delivering drug molecules to these macrophages because, following intravenous delivery, they are broken down by phagocytic cells in the body. The most well-known instances of this "Trojan horse-like" mechanism include any number of parasite illnesses, which typically affect the cells that make up the mononuclear phagocytic system. They consist of various fungal illnesses and leishmaniasis. N Over 100 million people worldwide suffer from leishmaniasis, a parasite infection of macrophages that is frequently fatal. The effective dosage of medications, which are primarily various antimonials, is not significantly less than the toxic dose. Liposomes provide an excellent drug delivery vehicle since they accumulate in the same infected cell population. In fact, when the medication was given to the rats in different liposome forms, the therapeutic index rose in the rats by up to several hundred times. Unfortunately, despite multiple extremely positive trials dating back to 1978, there was not much interest in clinically approving and scaling up the formulations. There are now a number of human studies using different antiparasitic liposome formulations underway. These formulations are derived from the highly successful and prolific field of liposome formulations in antifungal therapy, and they primarily use the ionophore Amphotericin B. Liposomes used as carriers for Amphotericin B in antifungal medicines have arguably produced the finest results in human therapy to date. This medication is the recommended treatment for widespread fungal infections, which usually result in death and frequently coexist with AIDS, chemotherapy, or weakened immune systems. Unfortunately, the medicine itself has a high level of toxicity, and its nephro- and neurotoxicity limits the dosage. These toxicities are typically connected with the drug's size or complexity, and it is evident that liposome encapsulation limits drug accumulation in these organs and significantly lowers toxicity. Moreover, the fungus frequently lives in the mononuclear phagocytic system's cells; as a result, encapsulation reduces toxicity and promotes passive targeting. However, these advantages are applicable to any colloidal drug carrier.In fact, stable mixed micellar formulations and microemulsions were found to provide comparable therapeutic benefits. Moreover, rather than being self-closing multilamellar liposomes, it appears that many of the early liposomal preparations were actually liquid crystalline colloidal particles. Since the first terminally sick patients' lives were spared since they did not react to all conventional therapies. Numerous patients were treated with a range of Amphotericin B formulations with great effectiveness. Antiviral and antibacterial treatments can be carried out using similar strategies.[9] However, the majority of antibiotics are taken orally, and liposome encapsulation should only be taken into consideration when

administering particularly strong and toxic antibiotics parenterally. Due to these molecules' interactions with bilayers and the high densities of their aqueous solutions, which frequently cause liposomes to float as a creamy layer on the top of the tube, the preparation of antibiotic-loaded liposomes at reasonably high drug to lipid ratios may be difficult. A number of additional approaches, including topical and pulmonary (by inhalation), are also being explored. Antivirals encapsulated in liposomes, such acyclovir, ribavarin, or azide thymidine (AZT), have also demonstrated decreased toxicity, and more thorough studies about their effectiveness are currently being conducted.[8]

4) Liposomes in Anticancer Therapy

It was demonstrated that numerous liposome formulations of different anticancer drugs were less harmful than the drug in its free form.[9] Anthracyclines are medications that primarily kill rapidly dividing cells by intercalating into the DNA to limit the growth of dividing cells. These cells are found in tumors as well as the mucosa of the gastrointestinal tract, hair, and blood cells; for this reason, this class of medications is extremely hazardous. Adriamycin is the most commonly used and researched drug (commercial name for Doxorubicin HCl). Its accumulated cardiotoxicity limits its dosage in addition to the acute toxicities already stated. Numerous formulas were experimented with Most of the time, there was a 50% reduction in toxicity. Because liposome encapsulation lessens the transport of the drug molecules towards certain tissues, this includes both acute and long-term toxicity. However, for the same reason, the drug's lower bioavailability frequently hindered its efficacy, particularly when the tumor was not phagocytic or was situated in an organ of the mononuclear phagocytic system. The sustained release effect of liposome encapsulation, or the prolonged persistence of therapeutic concentrations in the circulation, shown greater efficacy in certain situations, such as systemic lymphoma.[10] However, in a few other instances, the drug's effectiveness was actually diminished by its sequestration within the tissues of the mononuclear phagocytic system.Applications in humans shown generally lower toxicity, improved administration acceptability, and not very exciting efficacy.Various formulations are undergoing varying stages of clinical trials, exhibiting inconsistent outcomes.[11]

In Summary Let`s Discuss: - Liposome Production

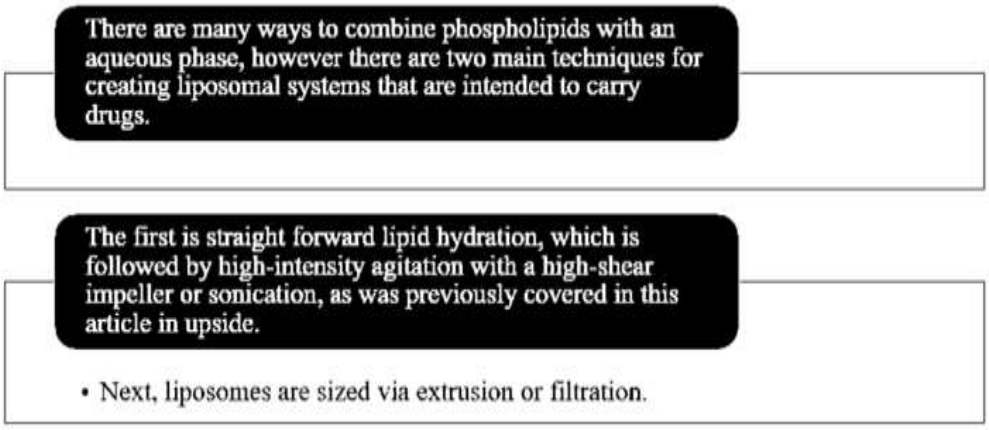

Figure No. 3: Summarizing Liposomes production by Lipid Hydration Method via High Intensity agitation including sonicator.

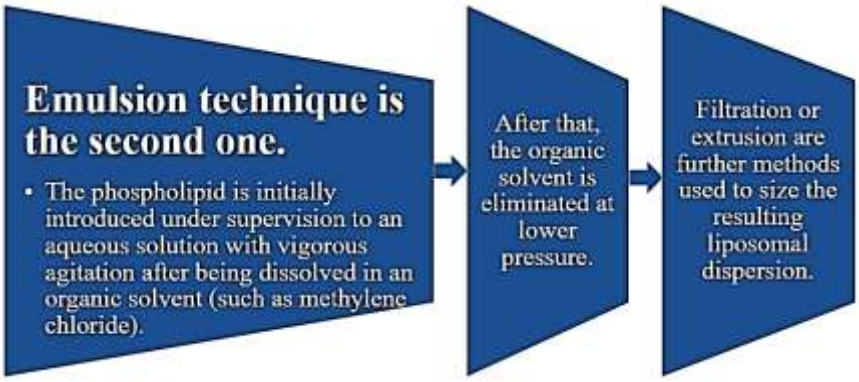

Figure No. 4: Summarizing Liposomes Production by Emulsion Technique.

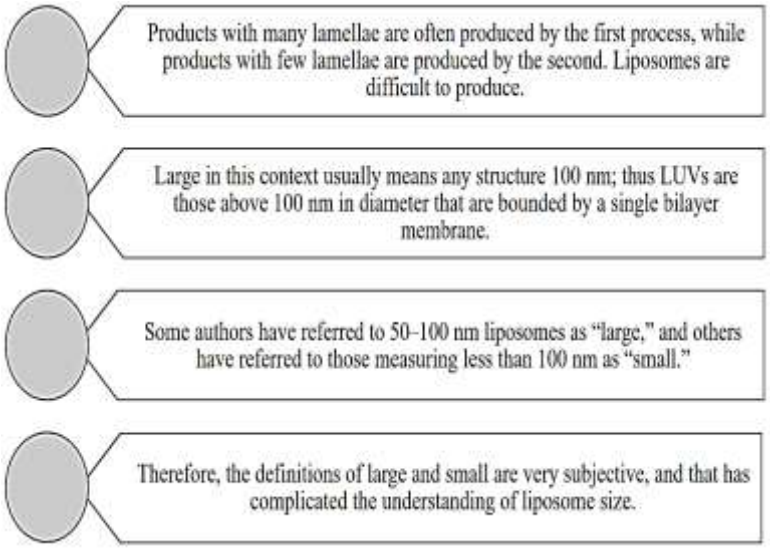

Figure No. 5: Summarizing Liposomes production and it`s size based knowledge and the definition of LUVs & SUVs.

Stability of Liposomes

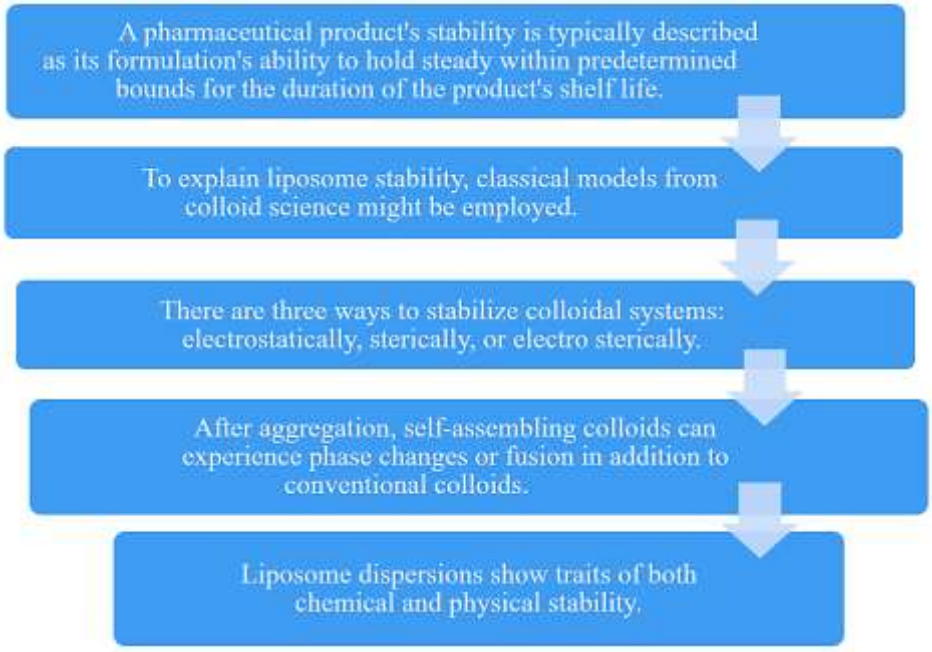

Figure No. 6: A Flow Chart supporting Stability of Pharmaceutical Delivery System: Liposomes.

In general, the chemical feature pertains to molecular structure, while the physical characteristic indicates the maintenance of liposome structure.

The amount of substance encapsulated and the liposome size distribution are both maintained in physically stable formulations.

The mechanical characteristics of the liposome membranes, as well as the system's thermodynamic and colloidal characteristics, all affect stability.

Liquid-dispersed system stability prediction is one of the trickiest issues formulation chemists deal with Scientists are frequently required to make decisions on experimental formulations or product shelf lives based only on rough estimates of how well they will endure over time.

Physical stability cannot be assessed using standardized tests, and the kind of stability being studied is frequently ambiguous.

CONCLUSION

At the final stage of our discussion holds during this journey of reviewing the Liposomes as the vesicular Drug Delivery Vehicle/ Carrier we`ve highlighted the introductory journery of

vesicles modernized delivery system, also provides the way that how the Lipomes works that means the significant mechanism of action of Liposomes, Also various kinds of Liposomes based Vesicles are there so we`ve catagorized these vesicles in two specific kinds Unilamellar liposome, Multilamellar Liposomes. Also this testimonal focused on limited manufacturing/production processes of Liposomes, we`ve well discussed that if you`ve proper facilities of sophosticated equipments like ultra-sonicator we can proceed with Sonication process of Liposomes production, also if we don`t have that level of sophosticated equipments we can proceed with Hand Shaking Method/ Simple Hydration Method. We`ve briefly discussed about how the drug loading should be performed we`ve given a pictorial based presentation of both the processes to be held during the same experiment. Also we tried to give our insights that nano carriers are not only in F & D but it also has application in day to day life diseases and made a tabular reperesentation of various kinds of approved nano delivery system too in form of liposomes. At last we can say we`vw tried to say in brief all about liposomes.

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