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Study of Effect of Lyophilization on The physicochemical stability of Liposome.

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ABSTRACT

Lyophilization is promising approach to increase the shelf life of liposome. The major limitation in the widespread use of liposome is its instability. The aim of this study was to investigate the effect of lyophilization either in the presence or in the absence of lyoprotectant on liposome properties Lyophilization is used to ensure an increased shelf life of liposomes by preserving them in dry state more stable than the aqueous dispersion. When stored as aqueous system the encapsulated drugs are released & the liposome might aggregate or fuse. The process of lyophilization without cryoprotectant resulted in particle size increased & significant content leakage. This review work suggests that the investigation of stability of lyophilized liposomes containing PC (Phosphatidyl Choline) & cholesterol. Liposomes sphere-shaped vesicles consisting of one or more phospholipids bilayer in which both hydrophilic & hydrophobic drug entity can be incorporated. Due to their size & hydrophobic & hydrophilic character liposomes are promising for drug delivery. This structure turns liposomes into ideal drug carriers, since hydrophilic drugs tend to entrapped in the core; while hydrophobic ones will be entrapped within the lipid bilayers. Liposome is one of the most successful drug delivery system applying nanotechnology to potentiate the therapeutic efficacy & reduce toxicities of conventional medicines. The encapsulation efficiency partially depends upon the logP of drug. Lyophilization is a strategy often employed to improve liposomal formulation stability, due to reactivity being far less pronounced in the solid versus aqueous state.

Keywords: Lyophilization, liposome, cryoprotectant, stability, increased shelf life.

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INTRODUCTION

Liposomes sphere-shaped vesicles consisting of one or more phospholipids bilayer in which both hydrophilic & hydrophobic drug entity can be incorporated. Due to their size & hydrophobic & hydrophilic character liposomes are promising for drug delivery. This structure turns liposomes into ideal drug carriers , since hydrophilic drugs tend to entrapped in the core ; while hydrophobic ones will be entrapped within the lipid bilayers. Liposome is one of the most successful drug delivery system applying nanotechnology to potentiate the therapeutic efficacy & reduce toxicities of conventional medicines. The encapsulation efficiency partially depends upon the logP of drug. Liposomes are micro particulate dispersion system whose size ranging from about 0.5-50µm in diameter. Therapeutic agents, most of which are anti-cancer drugs are encapsulated in the aqueous core or lipid bilayers of liposomes to improve their delivery to the targeted tissue. Lyophilization is a strategy often employed to improve liposomal formulation stability, due to reactivity being far less pronounced in the solid versus aqueous state. Lyophilization increases the shelf-life of liposomal formulation & preserves it in dries forms as lyophilized cake to be reconstituted with water prior to administration. To maintain the same particle size distribution after lyophlization a lyoprotectant needs to be added.

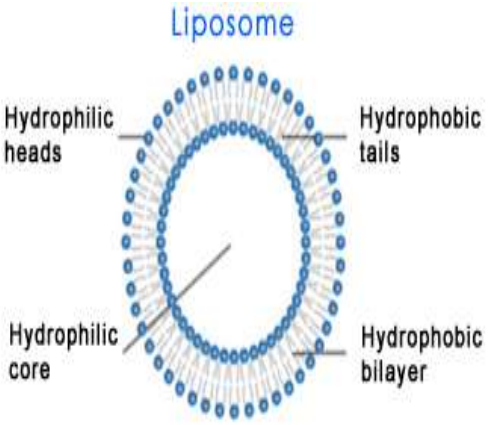

Figure 1: Structure of liposome

Advantages: [3, 4, 6, 7]

1. Liposome is increased efficacy & therapeutic index of drug.
2. Site avoidance effect.
3. Liposomes are helps to reduce exposure of sensitive tissues to toxic drugs.
4. They are biocompatible completely biodegradable, non-toxic, flexible & non-immunogenic for systemic & non-systemic administration.

5. Lyophilized liposomes increase the shelf life of liposomes by storing them in the dry state forms.

Disadvantages: [6, 7]

1. Liposomes may fuse or forms aggregates.
2. The production cost of liposomes is much more.
3. Liposomes having less stability compared to conventional dosage forms.
4. Quick uptake by cells of R.E.S.
5. Allergic reactions may occur to liposomal formulation.

LYOPHILIZATION: [1, 4,6]

Lyophilization or freeze drying is a process in which water is frozen, followed by its removal from the sample initially by sublimation (primary drying) & then by desorption (secondary drying). Freeze drying is a process of drying in which water is sublimed from the product after it is frozen. It is a drying process applicable to manufacturer of certain pharmaceuticals &biological that is thermo labile or otherwise unstable in aqueous solutions for prolonged storage periods, but that are stable in the dry state. The term "lyophilization" describes a process to produce a product that "loves the dry state."

Principle:

The main principle involved in freeze drying is a phenomenon called sublimation, where water passes through the liquid state. Sublimation of water can take place at pressures & temperature below triple point i.e. 4.579mm of Hg & 0.009 degree Celsius. The material to be dried is first frozen & then subjected under a vacuum to heat so that frozen liquid sublimes leaving only solid dried components of the original liquid. The concentration gradient of water vapor between the drying front & condenser is the driving force for removal of water during lyophilization.

Process To Produce A Product That "Loves Dry State":

Lyophilization allow drying of liposome at low temperature under conditions that allow removal of water by sublimation or change of phase from solid to vapor without passing through the liquid phase. Lyophilization is performed at temperature & pressure conditions below the triple point, to enable sublimation of ice. The entire process is performed at low temperature & pressure hence is suited for drying of thermo labile compounds. Steps involved in the lyophilization starts from sample preparation followed by freezing, primary drying, & secondary drying to obtain the final dried liposomes with desired moisture content .The concentration gradient of water vapor between the drying front & condenser is the driving force for removal of water during lyophilization.

The Lyophilization Process:

The lyophilization process consist of three stages: freezing, primary drying & secondary drying.

Freezing: During this stage the formulations is cooled. Pure crystalline ice forms from the liquid, thereby resulting in a freeze concentration of the remainder of the liquid to a more viscous state that inhibits further crystallization. Ultimately highly concentrated & viscous solution solidifies, yielding a amorphous, crystalline or combined amorphous-crystalline phase.

Primary Drying: This ice formed during freezing is removed by sublimation at sub ambient temperatures under vacuum. This step traditionally is carried out at chamber pressures of 40-400Torr & shelf temperature ranging from 30-10 degree celcius. Throughout this stage, the product is maintained in the solid state below the collapse temperature of the product in order to dry the product the product with retention of the structure established in the freezing step. The collapse temperature is the glass transition temperature in the case of amorphous product or the eutectic temperature for crystalline products.

Secondary Drying: The relatively small of bound water remaining in the matrix is removed by desorption. During this stage, the temperature of the shelf & product are increased to promote adequate desorption rates & achieve the desired residual moisture

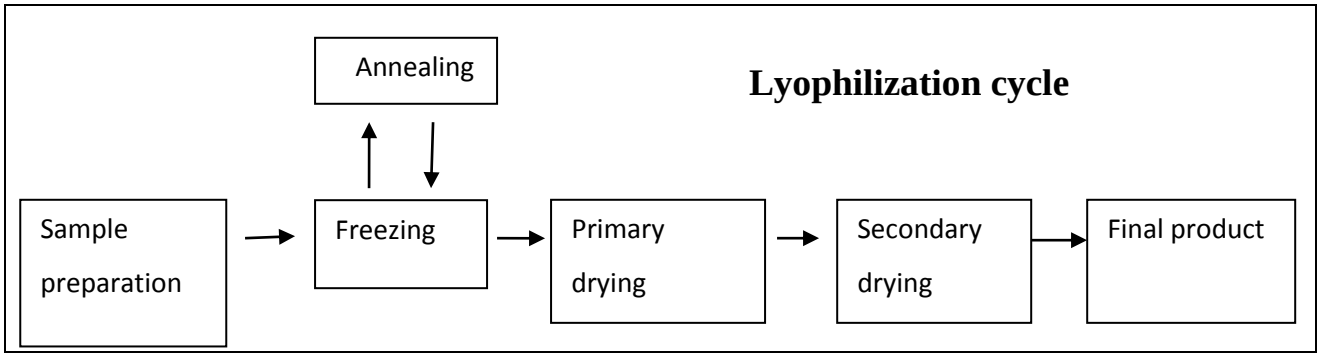

Figure 2: Lyophilization Cycle

Advantages of Lyophilization With Respect To Liposomes:

1. Chemical decomposition of liposomes is minimized.
2. Lipids used in the preparation of liposomes gets degraded at room temperature so the lyophilization also maintains the stability of lipids.
3. Removal of water without excessive heating.
4. Enhanced the stability of Liposomes in dry state.
5. Elegant cake appearances.
6. Lyophilization increases the shelf life of liposomes, by preserving them in dry state form.

7. Maintenance of the original characteristics of the Liposomes including their structure, surface morphology, particle size distribution.

Table 1: Target allowing with Drug as Liposomal Drug Delivery

1	Docetaxel Anhydrous	Taxotere	Long-circulating	Breast cancer	Phase I
2	Doxorubicin	Mycoset Doxil, Caelix	Non-PEGylated PEGylated	Breast cancer Caposis sarcoma,	Phase-III
3	Paclitaxel	LEP-ETU, Taxol, Abraxane	PEGylated	Breast cancer	Phase II

CONCLUSION:

Instability of Liposomes during storage are a serious limiting factor for their applicability as drug delivery system. Lyophilization is commonly used drying technique for thermo labile pharmaceuticals & also various studies demonstrate that lyophilization is an effective way to overcome the instability of Liposomes in the aqueous state. Lyophilization is often used to prepare liposomal formulation to achieve the commercially viable shelf lives. In the freeze dried liposome the chemical or physical reactions are inhibited or sufficiently decelerated, resulting in improved long term stability[1, 3, 5]. Besides the advantage of better stability, lyophilized liposome also provide ease of handling during shipping & storage. It is important to have a product of desirable quality & maintain physicochemical characteristics of formulation during storage. The resulting study suggests that there was no significant change in the drug content at 4°C and 25°C storage condition for 6months in lyophilized liposome with or without lyoprotectant.

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