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Lyophilization of Parenteral Dosage Form

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ABSTRACT : Now a days the Lyophilization process which is widely employed in Pharmaceutical Industry and additionally as Food Industry. Which helps to the improving the stability and long runs stability storage condition of a product. The parenteral routes are used for quick rapid drug action is preferred as an emergencies when the patient is unconscious, uncooperative , or uncapable to tolerate oral medications. The parenteral preparation includes injectable and transfusion fluids. The parenteral preparation should be sterile and non-pyrogenic in nature .this article provides an summary of parenteral preparations ,how the method of lyophilization and designing of freeze drying process.

KEYWORDS : Parenteral preparations, Method of Lyophilization, Design of freeze drying process .

INTRODUCTION

PARENTERAL DOSAGE FORM :

Sterile dosage form is those dosage form which are free from any dust fibres, microorganisms and foreign particles. It should be isotonic in nature. parenteral preparation as name derived from par +enteral are those administered by aside the enteral routes .

Parenterals are the dosage form which is directly injected into body tissue through the protective primary system of body ,skin, and mucous membrane. the parenteral preparations include injection ,transfusion fluids, suspension, sterile solids, sterile solutions ,and emulsions.

Parenteral preparation divided into two following varieties of preparations

1) Small Volume Parenterals (SVPs)
2) Large volume Parenterals (LVPs)

1) Small Volume Parenterals (SVPs) : as per U.S.P "an injection that's is packaged in containers labelled as containing 100ml or less".
2) Large volume Parenterals (LVPs) : In step with FDA are aqueous solutions which are packaged in volumes of at least 100ml with sizes of 250ml, 500ml, 1000ml and more. Examples are sodium chloride infusion, ringers, dextrose, plasma expanders etc.

IDEAL CHARACTERISTICS OF PARENTERAL DOSAGE FORM :

1)Sterility : The preparation should be free from all sorts of microorganisms.

2)Isotonicity: Parenteral preparations should be isotonic with blood plasma and body fluids.

3)Free from pyrogens : Preparation must be free from pyrogens and toxins .

4) Ready to use :

a) The dry soluble products able to combined with a suitable solvent before to use .

b) The dry insoluble products able to combined with a vehicle just before to use .

TYPES OF PARENTERAL DOSAGE FORM :

1) **solids dosage form :**The drugs are supplied as dry solids which are **Sterile** dissolved in a exceedingly solvent for administration into the body. these drugs are available in dry solids state because drugs aren't stable in solution form .

Example : Benzyl penicillin sodium injections .

2) **Transfusion fluids** : Parenteral solutions which are administered by intravenous route. Example : Sodium chloride , Ringers , Dextrose etc .

3) **Solutions /Emulsions :** Parenteral preparations are available in single dose container or multiple dose containers . Example : Nonsteroidal anti-inflammatory , Dexamethasone.

4) **Sterile suspensions :** Sterile suspension of medication during a suitable solvent and are administered by intramuscular route . Example : Hydrocortisone suspension, Methyl prednisolone .

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TYPES OF ADJUVANTS IN PARENTERAL DOSAGE FORM :

- Buffering agents
- Tonicity factors
- Stabilizers
- Solubility agents
- Emulsifying , suspending agents , and wetting agents
- Aqueous and Non-aqueous vehicle
- Aqueous vehicle – Water for injections are used .

Non-aqueous vehicle- Alcohols and Oils are used .

TEST FOR PARENTERAL DOSAGE FORM :

- Sterility Test
- Particulate contamination Test
- Bacterial endotoxin Test
- Pyrogen's Test
- Clarity Test
- Leakage Test
- Uniformity of drug content Test
- Uniformity of mass content Test

Containers and closure for parenteral dosage form :

The parenteral formulation is packed into containers ,which is created of glass and plastics. Container system includes vials, ampoules, syringe, bottles, bags, cartridges etc.

Ampoules are containing all glass whereas bags are containing all plastics .other containers may be composed of glass or plastics and that they include rubber materials , rubber stoppers for vails and bottles , rubber plungers and rubber seals for syringes and cartridges.

The containers or closure system depends on the several characteristics including container opening finishing ,closure models ,durometers compression set, and aluminium seal application force.

1) For Small Volume Parenterals (SVPs) : Ampoules , Glass vials sealed with rubber stoppers , Plastic ampoules (blow-fill-seal) ,pre-filled syringes , Needle-free injection.

2) Large volume Parenterals (LVPs) : Glass bottles sealed with rubber stoppers , Plastic bags.

LABELLING OF PARENTERAL DOSAGE FORM :

- Name and concentration of active substances
- Name and concentration of any added antimicrobial preservatives
- Route of administration
- Shelf- life
- Batch number
- Storage conditions
- Manufacturing address

ADVANTAGES OF PARENTERAL DOSAGE FORM :

- Rapid absorption and onset of action
- Fast onset action 15-30 seconds for intravenous route, 3-5 minute for intramuscular routes
- 100% bioavailability for intravenous routes
- Useful for unconscious and unable to acceptance of oral medication patients
- Useful for emergencies situations

Disadvantages Ofparenteral Dosage Form :

- Painful
- Costly
- Administered by train personnel only using aseptic procedures
- Preparation must be sterile
- If it not done properly , potentially harmful air bubbles can occur.
- If the needle is shared , there's is risk of HIV and lots of other infection disease

LYOPHILIZATION :

Lyophilization or freeze drying is a process of removing water by sublimation of ice crystals from frozen material. Generally, sublimation is considered as (primary drying) and desorption as (secondary drying).lyophilization or freeze drying it is referred as dehydration technique in pharmaceutical and diagnostic industry .in that dehydration technique the products are enables to liquid or slurry form, and that are previously frozen to be dried under a vacuum.

lyophilization technique is also known as cryodesiccation process.it is widely used in pharmaceutical and food products which helps to improve the stability as well as long term storage stability conditions of thermolabile drugs. The term lyophilization or freeze drying describe a process to assemble a product or produced a product that loves the dry state .it is applicable to manufacture a certain pharmaceutical and biological product , that are sensitive or unstable in aqueous solutions but they stable in their dry state for long shelf life

Lyophilization is most commonly method which is used in formulations of parenteral dosage

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forms .Lyophilization technique is a complex process that requires a careful balancing of equipment, product and processing method. lyophilization has been used to stabilize the many types of chemical components. The various biochemical components liquid in form , and they have biologically and chemically active , unstable , temperature sensitive, chemically reactive with each other, because of these characteristics components have very short life . since the improving the shelf life of that product we need to they refrigerated or degraded . the lyophilization solve the problem of reagents or components .The product which are unstable in solution form ,the term lyophilization gives long shelf life to product, then it stored in room temperature. This process gives excellent result in solubility ,characteristics and rapid reconstitution of product.

PRINCIPLE :

The process of lyophilization is a phenomenon called as sublimation , in which water is directly passes from solid sate to vapour state without passing liquid state .the sublimation of water can be take place at pressure and temperature . the temperature and pressure should be below the triple point .in that process the product has to be dried ,first frozen and then subjected to the heat at under high vacuum.(by conduction or radiation or both). So that the frozen liquid sublimes and dried solid by component remains only original present liquids .the driving force of sublimation of ice during process of lyophilization is the pressure difference between the vapour pressure of ice and partial pressure of water in the chamber .

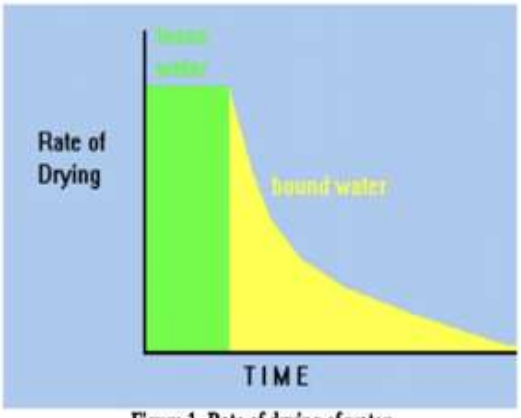

Figure 1: Rate of drying of water

PROCESS FOR LYOPHILIZATION :

Process of lyophilization can be done by four steps :

1)Pre-treatment

2)Freezing

3)

3) primary drying 4) secondary drying **1) Pre-treatment :**

In Pre-treatment methods the substance is before freezing . Pre-treatment includes the concentration of the product , addition of a component to extend the solubility and stability of the substance , preservation of the product appearance ,formulation to increasing the surface area and decreasing high vapour pressure level of solvents , formulations to stabilize reactive products .

2)Freezing :

Freezing is a process in which , change in state solid phase to gaseous phase. The material dried must be adequate prefrozen. in freezing the liquid sample is cooled until the get crystalline pure type of ice from the a part of liquid and sample is freeze concentration into a glassy state ,where is viscosity high and to permit the further crystallization .the method of freezing and final temperature of the frozen product is affect on the ability of the freeze product or dry material . during this method , the result of rapid cooling to make small crystal ice which are useful in preserving structured to examined microscopically ,but the products are difficult to dry. The result of slower cooling to make a bigger crystal ice which that have less restrictive channel matrix during the drying process. The freezing point can be determined by

Theoretical thermodynamic value

Cryo-microscope

DSC (Differential Scanning Calorimetry) Measurement of temperature and resistance during freezing phase .

Example of freeze -dried products are : antibiotics, bacteria, sera, vaccines, diagnostic medications, protein containing and biotechnological products, cells and tissues, and chemicals.

primary drying :

After the freezing the substance, the condition stabilized during which ice is far away from the frozen product via sublimation process and leading to dry ,structurally intact product .

primary drying requires two parameters - 1) Temperature 2) Pressure the rate of sublimation of ice from a frozen product that depends upon the difference in vapour pressure of the substance as compared to the vapour pressure of ice collector .

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In primary drying molecules are migrates from high sample to lower pressure sample area therefore the vapour pressure is expounded to temperature, and it's necessary that the substance temperature is warmer than the cold trap (ice collector) temperature . The temperature at which product is freeze dried is balance between the temperature and maintain the integrity of the frozen products and temperature that maximizes the vapour pressure level of product this is often balancing key of drying process .

In primary drying heat enters the products by one several mechanisms

1) By direct contact between container base and shelf , here the form of container is vital .
2) By the conduction process , the conduction across the container base and so through the frozen mass to the drying front it also referred to as sublimation interface.
3) By gaseous convection between product and residual gas molecules within the chamber .
4) By radiation, this is often low because of cold encountered in freeze-drying. Convection is certainly the foremost important of this mechanism.

4)Secondary drying :

After completion of primary freeze drying . the all ice has sublimed, and bound moisture continues to be present within the product . the substance appears dry but the residual moisture content present is also high as 7-8% therefore drying continued is important at warmer temperature to reduced the residual moisture content to optimum values . this process is thought as Isothermal Desorption . the bound water is desorbed from the substance .secondary drying is completed normally continued at product temperature over than the ambient but compatible with the sensitivity of the substance. In contrast to processing conditions for primary drying which use low shelf temperature and a moderate vacuum, desorption drying is facilitated by raising shelf temperature and reducing chamber pressure to a minimum. Care should be exercised in raising shelf temperature too highly; since, protein polymerization or biodegradation may result from using high processing temperature during secondary drying. Secondary drying is typically carried out for approximately 1/3 or 1/2 the time required for primary drying. The final practice in freeze-drying is to extend the shelf temperature during secondary drying and to decrease chamber pressure to all time low attainable level. the water is remaining during secondary drying is more strongly bound , and thus the require more energy for its removal. Decreasing pressure to the most attainable vacuum has traditionally been though to favour desorption of water .

FREEZE DRYER DESIGN :

The essential component of freeze dryer are

- Chamber
- Shelves
- Process condenser
- Refrigeration system
- Vacuum system
- Control system

Chamber :

This is the vacuum tight box, sometimes called the lyophilization chamber or cabinet. The chamber contains shelf or shelves for processing product. The chamber can also fit with a stoppering system. It is typically made of stainless steel and usually highly polished on the within and insulated and clad on the surface. The door locking arrangement by a hydraulic or motor.

Shelves :

The shelf act as a device or heat exchanger, removing energy from the substance during freezing, and supplying energy to the substance during the first and secondary drying segments of the freeze drying cycle. The shelves are going to be connected to the silicone oil system through either fixed or flexible hoses. Shelves will be manufactured in sizes up to 4 m^2 in area.

Process Condenser :

The process condenser is usually referred as just the condenser or the cold trap. It's designed to trap the solvent, which is sometime water, during the drying process. The process condenser will comprises coils or sometimes plates which are refrigerated to permit temperature. These refrigerated coils or plates is also an exceedingly vessel separate to the chamber, or they might be located within the identical chamber because the shelves. Hence there's designation "external condenser" and "internal condenser". Physically, the external condenser is traditionally placed behind the chamber, but it's going to be at the side, below or above.

The position of the condenser doesn't affect trapping performance. For an enclosed condenser the refrigerated coils or plates are placed beneath the shelves on smaller machines, and behind the shelves on larger

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machines, but again there's no performance constraint, only the geometry of the chamber. Shelf fluid system the freeze-drying process requires that the substance is first frozen and so
energy in the form of heat is applied **1)**throughout the drying phases of the cycle. This energy exchange is traditionally done by circulating a fluid through the shelves at a desired temperature. The temperature is about in an external heat exchange system consisting of cooling heat exchangers and an electrical heater. The fluid circulated is often silicone oil. This may be pumped around the circuit at a low pressure in a sealed circuit by means of a pump.

Refrigeration system :

The product to be freeze dried is either frozen before into the dryer or frozen whilst on the shelves. Compressors or sometimes-liquid nitrogen supplies the cooling energy. Most frequently multiply compressors are needed and therefore the compressor may perform two duties, one to cool the shelves and therefore the second to cool down the process condenser.

Vacuum system :

To remove solvent during a reasonable time, vacuum must be applied during the drying process. The vacuum level required are going to be typically within the range of fifty to hundred μ bar. To achieve such a low vacuum, a two stage rotary vacuum pump is used. . For large chambers, multiple pumps may be used .

Control system :

Control is also entirely or usually fully automatic for production machines.

The control elements required are as mentioned above, shelf temperature, pressure and time. A control program will set up these values as required by the substance or the process. The time may vary from some hours to many days.

FREEZE DRYING METHODS :

Manifold Method :

In the manifold method, flasks ampoules or vials are individually attached to the ports of a drying chamber. The substance either frozen in a freezer, by direct submersion in a low temperature bath, or by shell freezing, depending on the nature of the product and the volume to be freeze dried. The pre-frozen substance is quickly attached to the drying chamber or manifold to prevent warming. The vacuum must be created in the substance container quickly, and the operator relies on evaporative cooling to maintain the low temperature of the product.-eutectic and collapse temperatures.

Manifold drying has several advantages over batch tray drying. Since the vessels are attached to the manifold individually, each vial or flask has a direct path to the collector. This removes some of the competition for molecular space created in a batch system, and is most ideally realized in a cylindrical drying chamber where the distance from the collector to each product vessel is the same.

2) Batch Method :

In a batch drying, large numbers of similar sized vessels containing like substance are placed together in a tray dryer. The substance is usually pre-frozen on the shelf of the tray dryer. Precise control of the product temperature and the amount of heat applied to the product during drying can be maintained. Slight difference in heat input from the shelf can be expressed in different areas. Batch drying is used to prepare large numbers of ampoules or vials of one product and is usually employed in the pharmaceutical industry.

3) Bulk Method :

Bulk drying is usually carried out in a tray dryer like batch drying. However, the substance is poured into a bulk pan and dried as a one unit. Although the substance is spread throughout the entire surface area of the shelf and may be the identical thickness as substance in vials, the lack of empty spaces within the product mass changes the rate of heat input. The heat input is limited primarily to that provided by contact with the shelf.

EXCIPIENTS USED IN LYOPHILIZATION :

- Buffers
- Bulking Agent
- Stabilizers
- Tonicity Adjusters
- Antimicrobial Agents

EXAMPLES OF LYOPHILIZED PARENTRAL DRUG :

- Doxycycline Injection
- Colistimethate Injection
- Amphotericin B Injection
- Remdesivir Injection

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ADVANTAGES OF LYOPHILIZATION :

- Chemical decomposition is minimized.
- Removal of water without excessive heating.
- Enhanced product stability in a very dry state
- Ease of processing a liquid, simplifies aseptic handling.
- More compatible with sterile operations than dry powder filling.

DISADVANTGES OF LYOPHILIZATION :

- Increased handling and interval time .
- Volatile
- Equipment becomes costly and complicated
- Long-time process .

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