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AN OVERVIEW – FREEZE DRYING PROCESS OF PARENTERAL FORMULATION

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ABSTRACT

The freeze drying technique is most suitable process for the development of unstable drug for its betterment for use as parenteral formulation by intravenous administration. The product formed by the process has proper stability period for its administration with the help of diluent for its reconstitution. The dosage conditions must be variable depending upon the requirement of patient for its administration. The product formed after lyophilization process has the proper reconstitution time, and good appearance of the cake formation. Injection form allows administration of exact dose, as the absorption is complete. Injection form also cause quick onset of action which leads to faster relief and is most useful in cases of emergency and critical treatments.

KEYWORD: Product type and formulation, compatibility study, finished product testing, parenteral formulation

INTRODUCTION

Freeze drying (also known as lyophilization or cryodessication) is a dehydration process primarily used to preserve a degradable material or make the material more convenient for transport. Freeze drying works by freezing the material and then reducing the surrounding pressure and adding enough heat to allow the frozen water present into material to sublime

directly from the solid phase to gas. Lyophilized products are much difficult in comprising than other formulations in case of forming a uniform, solid mass which is stable throughout shelf life of product, present in elegant cake appearance. This is also useful to have short reconstitution time as well with clear solution after reconstitution and dried material does not stick to the walls of vial and stopper. Highly potent compounds deals particularly problematic when there is undissolved product observed due to potential dosing variation occurs after reconstitution. Thus, there is a need for a stable, uniform, readily reconstitutable, rapid acting injectable formulation with a relatively long shelf life, suitable for use in difficult to treat, agitated patients. Such formulation should be isotonic and reconstitutable in a small injection volume. [1,3]

Lyophilization or freeze drying is a process in which water is removed from a product after it is frozen and placed under a vacuum, allowing the ice to change directly from solid to vapor without passing through a liquid phase. The process consists of separate, unique, and interdependent processes; freezing, primary drying (sublimation), and secondary drying (desorption).

ADVANTAGES OF FREEZE DRYING

- Liquid can be easily processed for simple aseptic handling.
- Reconstituted liquid after Lyophilization is more stable than as such degradation material into liquid.
- Removal of water without excessive heating of the product
- Enhanced product stability in a dry powder
- Rapid and easy dissolution of reconstituted product

DISADVANTAGES INCLUDE

- Increased handling and processing time
- Need for Sterile Diluent upon reconstitution
- Cost and complexity of equipment

THE LYOPHILIZATION PROCESS INCLUDES FOLLOWING STEPS:

1. Transfer solvent generally water for Injection (WFI) in a glass vessel maintained at 20°C to 25°C
2. Add drug and excipients in sequence under continuous stirring and pH reading monitored for each addition.

3. Add (API) slowly and stir till it gets dissolved completely.
4. Make up the volume of bulk solution by using Water for Injection. Continue stirring. Ensure complete dissolution and check the clarity visually.
5. Filter the bulk solution through 0.45µm & 0.22 µm PVDF membrane filter.
6. Fill the bulk solution in suitable Clear/Amber glass vials for appropiate fill volume.
7. Stoppering & sealing operation to be done sparging head space nitrogen and vials sent for Lyophilization.
8. Freezing the solution by placing the partially stoppered containers on cooled shelves in a freeze-drying chamber or pre-freezing in another chamber.
9. Applying a vacuum to the chamber and heating the shelves in order to evaporate the water from the frozen state.
10. Complete stoppering of the vials usually by hydraulic or screw rod stoppering mechanisms installed in` the lyophilizers

DESIRED CHARACTERISTICS OF LYOPHILIZED PRODUCT

A lyophilized product should possess certain desirable characteristics, including

- Long-term stability
- Short reconstitution time
- Elegant cake appearance
- Maintenance of the characteristics of the original dosage form upon reconstitution, including solution properties; structure or conformation of proteins; and particle-size distribution of suspensions
- Isotonicity upon reconstitution (in some cases, also for bulk solution).

PARENTERAL DOSAGE FORM

The term Parenteral is derived from the Greek words *para*, meaning beside, and *entron*, meaning intestine, which together indicate something done outside of the intestine and not by way of the alimentary tract. A drug administered parenterally is one injected through the hollow of a fine needle into the body at various sites and to various depths. The three primary routes of Parenteral administration are subcutaneous, intramuscular (IM), and intravenous (IV) although there are others such as intracardiac and intraspinal. [4]

ADVANTAGES

1. Drugs destroyed or inactivated in the gastrointestinal tract or too poorly absorbed to provide satisfactory response may be parenterally administered.
2. The parenteral route is also preferred when rapid absorption is essential, as in pregnancy situations.
3. Absorption by the parenteral route is not only faster then oral administration, but the blood levels of drug that result are far more predictable, because little is lost after subcutaneous or intramuscular injection, and virtually none by intravenous injection, this also generally permits the administration of smaller doses.
4. The Parenterals are useful in treatment of patients who are uncooperative, unconscious or otherwise unable to accept oral medication.

DISADVANTAGES

1. Once the drug is given by the parenteral administration, there is no retreat. That is, once the substance is within the tissues or is placed directly into the blood stream, removal of the drug warranted by an untoward or toxic effect or an in advertent overdose is most difficult.
2. By other means of administration, there is more time between drug administration and drug absorption which becomes a safety factor by allowing for the extraction of unabsorbed drug.
3. Also, because of strict sterility requirements for all injections, they are more expensive than other dosage forms and require competent trained personnel for their proper administration

PARENTERAL FORMULATIONS

SMALL VOLUME PARENTERALS [3]

The term small volume parenteral (SVP) has been officially defined by USP as an injection that is packaged in containers labeled as containing 100 ml or less. The USP categorizes sterile preparations for parenteral use according to physical state of the product as follows-

1. Solutions or emulsions of medicaments suitable for injection
2. Dry solids or liquid concentrates containing no additives which upon the addition of suitable solvents, yield solutions conforming in all respects to requirements for injections
3. Preparations the same as in class 2 but containing one or more additional substances

4. Suspensions of solids in a suitable medium which are not to be injected intravenously or into the spinal column
5. Dry solids which upon the addition of suitable vehicles become sterile suspensions.

LARGE VOLUME PARENTERALS [3]

The USP provides the definition for large volume parenterals (LVPs) "the designation large volume solution applies to an injection that is intended for intravenous use and is packaged in containers holding 100 ml or more."

Formulations have been developed to

1. Supply the water, electrolytes, and simple carbohydrates needed by the body
2. Act as the vehicle for infusion of drugs that are compatible in the solution
3. Supply nutritional requirements when the nutrients can not be taken orally
4. Provide solutions to correct acid-base balance in the body
5. Act as plasma expanders
6. Promote diuresis when the body is retaining fluids
7. Act as dialyzing agents in patients with impaired kidney function
8. Act as x-ray contrast agents to improve diagnostic abilities

STEPS INVOLVED IN THE FORMULATION OF PARENTERAL DRUG PRODUCT

1. Obtain physical properties of active drug substance

- Structure, molecular weight
- Practical solubility in water at room temperature
- Effect of pH on solubility
- Unusual solubility properties

2. Obtain chemical properties of active drug substance

- Must have validatable analytical method for potency and purity
- Time for 10% degradation at 5^0C
- pH stability profile
- Sensitivity to oxygen
- Sensitivity to light
- Major routes of degradation and degradation products

3. Initial formulation approaches

a. Timeline for drug product

b. Use of drug product

- Single dose vs. multiple dose
- Shelf life goals
- Combination with other products, diluents

c. From knowledge of solubility and stability properties, and information from anticipated clinical use formulate drug with components and solution properties that are known to be successful at dealing with these issues. Then perform accelerated stability studies.

- High temperature storage
- Temperature cycling
- Light and/or oxygen exposure
- For powders, expose to high humidities

d. Short term stability studies

e. Container and closure requirement

f. Design and implement an initial manufacturing method of the product

g. Finalize formulation

COMPATIBILITY STUDY OF PARENTERAL FORMULATION

The Formulation development based on compatibility study of prepared bulk solution for parenteral administration which includes:

- Silicon tubing compatibility
- Filters compatibility
- Metal (SS 316L) compatibility.
- Freeze thaw study.
- Photostability study
- Stopper compatibility.

Details of formulation development studies, compilation of development trials & related recommendations to manufacturing are discussed in the following section.

SILICON TUBING COMPATIBILITY

In this, effect of Silicon Tubing on Optimized Bulk solution of Lyophilized Formulation. In pharmaceutical manufacturing, silicone tubing is typically classified as a process aid. It is used in transfer processes and as such should not interact with the drug product. SaniTech tubing from Saint-Gobain was used for transfer process. It is manufactured from the fine

grade of silicone materials and is fully characterized, validated and tested to a variety of specifications. It is ultra-pure biopharmaceutical-grade tubing. SaniTech platinum-cured silicon tubing resists temperature extremes, ozone, radiation, moisture, compression sets, weathering and chemical attack, and imparts no odors to fluids transported within it. Silicon tubing withstands repeated autoclaving and sterilization methods. Some benefits of are:-

- Ultra-pure biopharmaceutical-grade silicon.
- Unsurpassed surface smoothness.
- Ultra flexible.
- Autoclavable and Sterilizable.
- Temperature range from: 80°F (62°C) to 500°F (260°C).
- Imparts no taste or odors.
- Meets USP Class VI and USFDA criteria.

METAL COMPATIBILITY

Compatibility Study of Bulk solution of Lyophilized Formulation with Metal (SS 316L)

The bulk solution to divide into two parts (Part A: - Unfiltered & Part B: - filtered). Sufficient quantity of unfiltered and filtered samples required for Metal (SS 316L) sensitivity and holding time study on unfiltered/filtered bulk solution.

FILTER COMPATIBILITY

Compatibility Study of Bulk solution of Lyophilized Formulation with Filters (0.45µand 0.22µ PVDF filters) Divide the final bulk solution into two parts (Unfiltered & filtered). Sufficient quantity of unfiltered and filtered samples required for hold time study for time intervals and later analytical testing.

FREEZE THAW STUDY

Vial filled of lyophilized formulation charge in the cold storage maintained at temperature between 2ºC to 8°C for 2 days. On 3rd day remove all the vials from the refrigerator. Place the above samples in the 25°C ± 2°C / 60 ± 5 % RH chambers for 2 days. On 5^{th} day remove all the vials from the 25°C ± 2°C / 60 ± 5 % RH stability chamber. Store them in cold storage maintained at temperature between 2ºC to 8°C for 2 days. On 7^{th} day remove all vials from the cold storage. Place them in the 25°C ± 2°C / 60 ± 5 % RH chamber for 2 days. On 9^{th} day remove all the vials from the 25°C ± 2°C / 60 ± 5 % RH stability chamber. Store them in cold storage maintained at temperature between 2ºC to 8°C for 2 days. On 11^{th} day remove all the

vials from the cold storage. Place them in the 25°C ± 2°C / 60 ± 5 % RH chamber for 2 days and later analytical testing.

PHOTOSTABILITY STUDY

Samples of Bulk solution of Lyophilized Formulation expose to light providing an overall illumination of not less than 1.2 million lux hours and an integrated near ultraviolet energy of not less than 200 watt hours/square meter.

STOPPER COMPATIBILITY

Divide the final bulk solution into two parts (Part A: - Unfiltered & Part B: - filtered). Sufficient quantity of unfiltered and filtered samples to keep with stoppers and testing to the analytical laboratory for initial analysis.

FREEZE DRYING PROCESS

Freeze-drying is a widely used process for drying and improving the stability of various pharmaceutical products including: viruses, vaccines, proteins, peptides or colloidal carriers liposomes, nanoparticles, nanoemulsions. This process is relatively slow and expensive, it is especially applies only for products having a high added value. Freeze-drying cycle can be divided into three steps: freezing (solidification), primary drying (ice sublimation) and secondary drying (desorption of unfrozen water).[6,7]

FREEZING

It is important to remember that freezing the product decreases chemical activity by decreasing molecular movement and is essentially the dehydration step in freeze-drying. Once the solvent matrix is in the solid (frozen) state the solute matrix is "dry". In order to freeze a product properly, thermal analysis of the product must be conducted. Water has a freezing point of 0C. Almost any product that has a constituent other than water will experience a heat of fusion/crystallization not only around 0C but also at a reduced temperature.

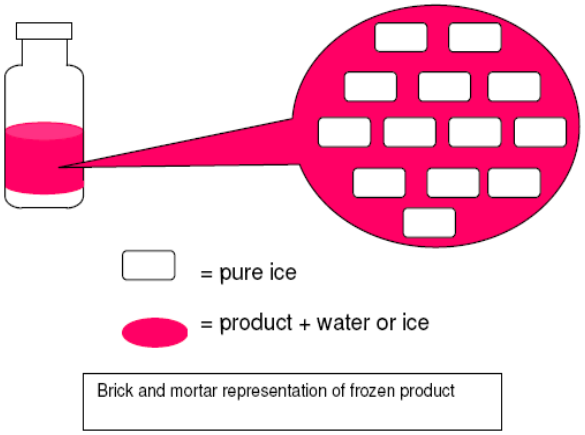

Fig 1. Brick and mortar representation of frozen product

In the product matrix there is essentially "unbound or free" solvent. This is the solvent that is not closely associated with the product itself. The solvent that is more closely associated with the product will freeze at some reduced temperature. The reduction in freezing point of the solvent may be due to weak solvent/solute bond formation or may be caused by the actual entrapment of the solvent molecule in the solute (as is possible with large protein molecules). The freezing of the product may result in either a eutectic or a collapse. The eutectic temperature equates to the triple point of the product on the phase diagram. In this instance the product is frozen in the classic sense. In some product systems the mobility of the product, located in between the frozen ice crystals, slows down considerably. Prior to freeze drying the mobility in this area must be as small as possible in order to support the freeze drying process. [7]

In order to freeze dry a product, in the perfect sense of the word, the product temperature must be maintained below its lowest freezing point during the entire Primary Drying step.

PRIMARY DRYING

There are 3 basic components of any freeze dryer. These components are the product addition station, the condenser and the vacuum pump. Each component is vital in the function of the freeze dryer.

There are two basic types of product addition stations, manifolds and shelves. If a product is relatively sophisticated, chemically complicated, subject to resale or aseptic processing a tray dryer should be used for freeze-drying. When using a tray dryer the researcher has ultimate

control over the parameters that drive the freeze-drying process. If the product is relatively simple in nature, has proven to be easy to freeze dry, is for in-house use or only small amounts are processed a manifold system may be used.

With manifold systems a prefrozen product is introduced to the freeze dryer that has a condenser temperature of -40°C or lower and is at a low pressure (usually below 500 mT). When using a manifold system it is important that the vapor path between the product and the low temperature condenser be as direct as possible and free from obstruction. When a product is to be processed in a tray dryer the product containers are loaded into trays for introduction to the freeze dryer. If the product has been prefrozen the shelves of the tray dryer should be pre-cooled to a temperature slightly below the freezing point of the product. In most cases the room temperature product is introduced to room temperature shelves of the tray dryer. The tray dryer refrigeration is then activated to freeze the product. [7]

The vacuum pump of a freeze-dryer serves, during Primary Drying, to remove noncondensable vapors from the freeze dryer. Noncondensable vapors are present during the initial evacuation of the system and during the freeze dry run due to leaks in the equipment and the constant release of noncondensables in the product as freeze-drying progresses.
In order for a freeze dryer to be effective the temperature of the condenser must be lower than the temperature of the product. This temperature differential creates a pressure differential and the net migration of water vapor is towards the condenser. Another driving force of sublimation is the temperature differential between the product at the freeze-dry and ice interface and the surface closest to the heat source (eg. the shelves). The temperature of the product at the freeze dry and ice interface is dictated by the pressure in the system.

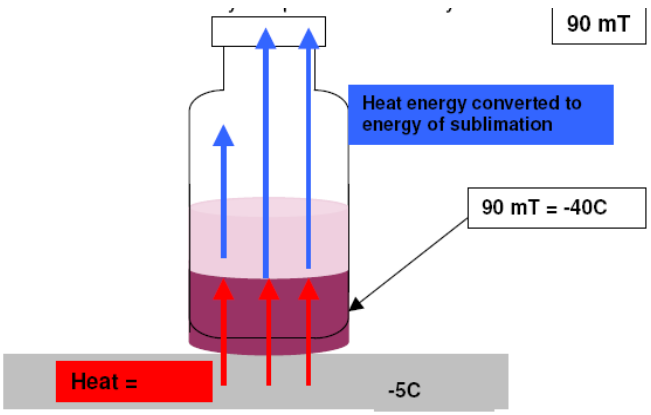

Fig 2. Primary Drying

It is important to remember however that heat input constraints are often caused by the product's own thermal characteristics. If a product has a melting temperature of -10°C the temperature of the product may be taken to a temperature of approximately -15°C. If the condenser is -54°C this will result in a pressure differential of 1223 mT. This will result in a faster transfer of water vapor out of the product than if the product temperature were left at –40°C. As water vapor migrates from the product to the condenser the concomitant energy held by the water vapor is released to the refrigeration system of the condenser. This will often result in an increase in the condenser temperature. Condenser design and efficiency is consequently of paramount importance in the Freeze-drying cycle. [7]

Typically, in freeze-drying cycles the product temperature will lag behind the shelf temperature. During Primary Drying, this temperature lag produces an increase in the cycle time. Many researchers believe that by increasing the pressure in the system the number of molecules available for heat transfer from the heat source (the shelves) to the product is increased and the thermal lag is minimized. Additionally the use of removable bottom trays will decrease on the number of heat transfer barriers between the shelves and the product.

Regardless of the method of freeze-drying employed it is essential to remember that Primary Drying is an often delicate balance between the energy input to the product and the pressure differential created between the product and the condenser due to the temperature differential.

SECONDARY DRYING

When the product reaches a temperature above 0°C Secondary Drying has begun. During Secondary Drying the vacuum pump creates the low pressure condition necessary for the removal of solvents and the condenser acts as a trap for those solvents. A product in Secondary Drying often appears dry. The solvent being removed during this step is referred to as "bound". The amount of residual water in the product is dependent on the length of time the product remains in Secondary Drying. There is no condensate on the outside of the flask and the flask is a room temperature. This indicates that there is no longer any energy transfer from the ambient conditions to the product. The condenser temperature has returned to its original low temperature. This indicates that the condenser is no longer trapping enough vapors and its associated energy to result in a condenser temperature rise. The pressure in the system has returned to its original low value. Once again this indicates that the movement of vapor molecules has decreased substantially.

If conditions are met, and the product continues to freeze dry for another 6 hours but the residual water Content remains too high it must make a judgment about how much more time should be added to this step of freeze-drying. [7]

Once the product is determined to be at the end of its cycle it must be removed from the freeze dryer. On manifold systems atmospheric pressure is bled into the product container to allow easy removal, of the container, from the valve. It is important to remember that the now dry product will act like a "sponge" and draw water from the ambient conditions to which it is exposed. Consequently it should be processed or capped off and stored as soon as possible.

PRODUCT TYPE AND FORMULATION-

Products are manufactured in lyophilized form due to their instability when in solution. Many antibiotics, such as some of the semisynthetic penicillins, cephalosporins, and some of the salts of erythromycin, doxycycline, and chloramphenicol, are made by the lyophilization process. Because they are antibiotics, low bioburden of these formulations would be expected at the time of batching. However, some of the other dosage forms that are lyophilized, such as hydrocortisone sodium succinates, and many of the biotechnology-derived products, have no antibacterial effect when in solution.

For these types of products, bioburden should be minimal; the bioburden should be determined prior to sterilization of these bulk solutions should be controlled to prevent any increase in microbiological levels that may occur up to the time the bulk solutions are filtered (sterilized). The concern with any microbiological level is the possible increase in endotoxins. Good practice for the compounding of lyophilized products would be also include batching in a controlled environment and in sealed tanks, particularly if the solution is to be held for any length of time prior to sterilization.

In some cases, manufacturers have performed bioburden testing on bulk solutions after prefiltration and prior to final filtration. Although the testing of such solutions may be meaningful in determining the bioburden for sterilization, it does not provide any information regarding the potential formation or presence of endotoxins. The testing of 0.1-mL samples by LAL methods of bulk solution for endotoxins is of value, but testing of at least 100 mL size samples prior to prefiltration, particularly for the presence of Gram-negative organisms, would be of greater value in evaluating the process. For example, the presence of

Pseudomonas species in the bioburden of a bulk solution has been identified as an objectionable condition.

FINISHED PRODUCT TESTING [4]

Several aspects of finished product testing are of concern to the lyophilized dosage form. These include dose uniformity, moisture and stability testing, and sterility testing.

DOSE UNIFORMITY

It mainly includes two types of dose uniformity testing: content uniformity and weight variation. It states that weight variation may be applied to solids, with or without added substances that have been prepared from true solutions and freeze dried in final containers. However, when other excipients or other additives are present, weight variation may be applied, provided there is correlation with the sample weight and potency results. In order to determine potency, it is common to reconstitute and assay the entire contents of a vial without knowing the weight of the sample. Performing the assay in this manner will provide information on the label claim of a product, but without knowing the sample weight one has no information about dose uniformity. One should correlate the potency results obtained from the assay with the weight of the sample tested.

STABILITY TESTING

It is obvious concern with the lyophilized product that there is amount of moisture present in vials. With other dosage forms, the expiration date and moisture limit should be established based on worst case data. That is, a manufacturer should have data that demonstrate adequate stability at the moisture specification. As with immediate release potency testing, stability testing should be performed on vials with a known weight of samples. For example, testing a vial (sample) which had a higher fill weight (volume) than the average fill volume of the batch would provide higher potency results and not represent the potency of the batch. Also, the expiration date and stability should be based on those batches with the higher moisture content. Such data should be considered in the establishment of a moisture specification.

For products showing loss of potency due to aging, there are generally two potency specifications. There is a higher limit for the dosage form at the time of release. Stability testing should also include provision for the assay aged samples and subsequent reconstitution of these aged samples for the maximum amount of time specified in the labeling. In addition to this stability testing of reconstituted solutions should indicate the most

concentrated and least concentrated reconstituted solutions. The most concentrated reconstituted solution will usually exhibit degradation at a faster rate than less concentrated solutions.

STERILITY TESTING

With respect to sterility testing of lyophilized products, there is concern with the solution used to reconstitute the lyophilized product. Though products may be labeled for reconstitution with bacteriostatic Water for Injection (WFI), sterile WFI should be used to reconstitute products. It is useful to implement with bacteriostatic WFI because of the potential toxicities associated with it. Bacteriostatic WFI may kill some of the vegetative cells if present as contaminants, and thus mask the true level of contamination in the dosage form. As with other sterile products, sterility test results that show contamination on the initial test should be identified and reviewed.

CONCLUSION

The review was presented to focus development and optimization of the processing of bulk solution for parenteral administration and further freeze drying the product with appropriate temperature, vacuum and pressure conditions across stages of freeze drying so that formulation can be prepared at suitable optimized lyophilized conditions without affecting quality of formulation. The performance of manufacturing and testing process for lyophilized formulation was detailed out and should be feasible for the development.

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