PHARMSOL NEWS

LYOPHILIZATION - A PREFERRED APPROACH TO INJECTABLE DOSAGE FORM

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Parenteral products are the best alternative to the solid oral dosage forms specifically for the patients who are bedridden and faces challenge in swallowing the solid oral dosage forms. Among the Parenterals, lyophilized injectables are the best alternative which are most prescribed to attain the maximum bioavailability and stability. Most of the complex APIs and biologics faces challenges with respect to the formulation stability which in turn resulted in manufacturers turning to lyophilization over the past few years.

As per the reported literature, it is estimated that over 50% of biologics on the market today would not be possible without lyophilization, and market demand for lyophilization technology will only increase as more injectables, biosimilars and novel biologics are developed.

What are Lyophilized Injections:

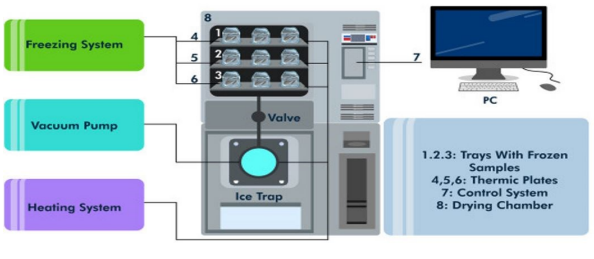
Lyophilized injections are manufactured in a sterile environment at low temperatures using a vacuum, which results in sublimation to remove water in pre-frozen drug solution by changing their state directly from solid (ice) to gas (vapor).

Advantages

- Ideal drying technique for heat sensitive & oxidative sensitive products
- Stable in dry state and reconstitution stage along with increased shelf life.
- Products are sterile and free form pyrogen.
- Sufficient strength to last for a long time and easier to ship for transportation.
- Easily packaged and transferred as a finished product.

Lyophilization equipment-

It includes four basic components a drying chamber, a vacuum pump, a heat source, and a condenser. The correct selection and operation of these components are critical to reach the benefits of the lyophilization process and depend on the requirements of each product.

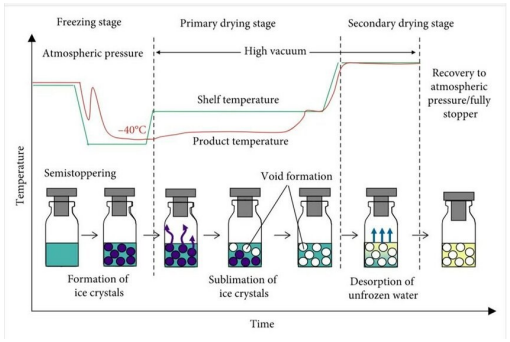


Brief Lyophilization process:

It generally includes three steps after sample preparation generally using Water for Injection

1. Freezing stage: In this stage, the water or solvent in the partially stoppered glass vials is gradually frozen by cooled shelves which can be easily removed by sublimation.
2. Primary Drying (Sublimation): During this step, temperature and pressure are manipulated to convert water directly from solid to gas via sublimation, and the resulting water vapor is collected on a condenser.
3. Secondary Drying (Desorption): During this step, the shelf temperature in the is gradually raised under low pressure to drive off residual water or solvent. In this step diffusion and desorption of non-freezing water occur in the product. It is an indispensable step in lyophilization because the remaining water deteriorates the quality of products.The glass vials shall be fully stoppered after the desorption of unfrozen water.

It's a complex interplay of several factors like vapor pressure, Eutectic temperature, triple point each having a profound impact on the process's efficiency and the product's final quality:



Mfg. flow of Lyophilization Process

Manufacturing of the lyophilized Injectable product:

Development and Manufacturing of lyophilization products may involve only API along with WFI for mixing or may require addition of drug-specific excipients such as stabilizers, buffers, isotonic agents, surfactants, solvents, and bulking agents to solubilize the API, maintain the desired pH, support the cake appearance, and ensure long-term stability of the drug product.
Along with the composition, compatibility studies with packaging components (glass vials, stoppers, caps) and manufacturing components (tubing, bags, needles) need to be critically studied.

Following are the CMA, CPP and CQA which required to be thoroughly studied for successful development of the lyophilized product.

Critical material attributes (CMA's)	Critical process parameters (CPP's)	Critical quality attributes (CQA's)
Buffer	Shelf temperature	Cake appearance
Surfactant	Freezing ramp rate	Reconstitution time
Fill volume	Freezing temperature	pH
Total solid content	Hold time for freezing	Residual moisture content
Ionic strength	Chamber pressure at primary drying	Potency
Configuration of vial	Ramp rate to primary drying hold	Concentration of solution
Stopper	Primary drying temperature	Particulate matter
–	Hold time for primary drying	Content uniformity
–	Ramp rate to secondary drying hold	Drug impurity
–	Secondary drying temperature	Sterility
–	Hold time for secondary drying	–

Optimization of the composition along with CPP at each stage is important because these can have a direct impact on the process efficiency (shortened cycle time) and product performance (cake appearance and homogeneous moisture content).
Overall, the product needs to be manufactured in aseptic and sterile areas with regulatory requirements of safety, sterility, pyrogenicity, particulate matter, stability, compatibility, and isotonicity.

Containers and closures for lyophilized Injectable products:

Lyophilized drugs must be packaged in an air-tight aseptic container to prevent moisture from entering which can promote degradation over shelf life. Other factors which need to be considered are compatibility with the product, material of construction and proper functionality of the container/device for their intended use. Glass Vials, Ampoules Syringes and Dual chamber devices are commonly used as containers for lyophilized products.

Closures (screw caps, stoppers, etc.) must satisfy all the functions required of the container along with additional requirements such as seal integrity and reseal properties along with low surface tackiness during processing.

Conclusion:

Lyophilization is considered as a breakthrough process with commercial viability, however it involves complex formulation and manufacturing challenges during development, optimization, scale-up and transfer of lyophilization cycles, which require an extensive work to understand the critical material attributes and process parameters to achieve desired quality attributes of the product.
PharmSol helps in providing customized solutions for individual products with its large portfolio of development of lyophilization processes alongside process analytical technologies ensure the highest product quality.

How PharmSol can help you?

PharmSol can provide integrated and customized services for the development of Lyophilized products with focus on

- Development and tech transfer of lyophilized solid and injectable products
- Regulatory services for Filing dossier of the finished products
- Setting up of sterile manufacturing facility with required Regulatory certification (EU, US etc.)

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