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Review Article

LYOPHILIZED INJECTION: A MODERN APPROACH OF INJECTABLE DOSAGE FORM

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ABSTRACT

Now-a-days, lyophilized injection dosage form is extensively used to improve the bioavailability, stability, solubility and patient compliance. The lyophilized injection has considered as alternative to oral solid dosage forms for better patient compliance especially in bed ridden patients and for attaining maximum bioavailability, improved stability. The lyophilized injection reconstitute before injection to produce liquid injection. This review includes a detailed updated concept on lyophilized injection.

Keywords: Lyophilized injection, parenteral, freeze drying

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INTRODUCTION

A drug is defined as agent intended for use in the diagnosis, mitigation, treatment, cure or prevention of disease in humans or in other animals (Food drug and cosmetic Act, 1938). A new drug is needed to be approved by Food and Drug Administration (FDA) before it introduces into a research.¹ Before introducing into the market, the sponsor (pharmaceutical company) should provide supporting scientific evidence to state that drug is safe and effective in all ways. The process between the drug discovery and its approval is time consuming process, but it's necessary before it going for formulation development.²

USP general chapter for parenterals³⁻⁴

Parenteral:

Parenteral articles are preparations intended for injection through the skin or other external boundary tissue, rather than through the alimentary canal, so that the active substances they contain are administered, using gravity or force, directly into a blood vessel, organ, tissue, or

lesion. Parenteral articles are prepared scrupulously by methods designed to ensure that they meet Pharmacopeia requirements for sterility, pyrogens, particulate matter, and other contaminants, and, where appropriate, contain inhibitors of the growth of microorganisms. An Injection is a preparation intended for parenteral administration and/or for constituting or diluting a parenteral article prior to administration. Parenteral route of drug administration is most favorable for highly potent and low dose of drug. The various route of administration available among them intravenous route give highest systemic circulation of drug and able to achieve 100% bioavailability of drug.

Advantages

- i. Parenteral route is rapid
- ii. Useful for unconscious patients
- iii. Useful in case of uncooperative patients
- iv. Inactivation by GIT enzymes can avoid
- v. First pass effect is avoided
- vi. Bioavailability is 100%

Disadvantages

- i. Painful
- ii. Need skill
- iii. Method is expensive
- iv. It is less safe

Lyophilized Injection

Lyophilization is the recent most commonly used method for manufacturing parenteral when aqueous solution stability is a major issue. It is central to the protection of materials, which require low moisture content (less than 1%) in order to ensure stability and require a sterile and gentle preservation process. Lyophilization produces excellent quality products, both for foodstuff and pharmaceuticals, due to the moderate temperatures at which the process takes place, contributing to the formation of highly porous solids that retain aroma, colour, and flavour.⁵⁻⁷

In lyophilization process vacuum takes place at very low pressures so that the operation occurs below the triple point of water, leading to high investment and operating costs.⁷ Freeze-drying is a process, in which a product is frozen and then dried by sublimation of the ice. The total process involves four steps: freezing; sublimation of the ice, called main drying (MD); desorption of the water bound to the solid, called secondary drying (SD); and packing in containers to exclude absorption of water and/or oxygen from the atmosphere⁸. By freeze-drying a product unstable in water is transformed into a dry, stable product. The process has to be developed to satisfy four demands on the Rinsed product: its volume remains that of the frozen substance; the structure and the biological activity of the dried solid correspond as far as possible to those of the original substance; the dried product remains stable during storage, if possible at temperatures up to +40°C and for up to 2 years; and with the addition of water the original product is quickly reconstituted⁹.

Characteristic of freeze-dried product

- ❖ Sufficient Strength
- ❖ Uniform color
- ❖ Sufficient Porous and dry
- ❖ Sterile, Free from pyrogen
- ❖ Free from Particles
- ❖ Stable in Dry and Reconstitution Stage

Principles of freeze drying¹⁰

1. Heat transfer

Heat supplies the energy sufficient for the evaporation of water by sublimation. An ice crystal composed of pure water. Many molecules have natural vibrations. So we are giving extra energy for water molecules to break free. After freeing, water molecules sublimates from the surface of solid and outer surface of sample got thickened. Then, more energy is required for the

transportation of water molecules to the surface. Heat transfer to the product achieves in three ways;

- a. Direct conduction
- b. Gas conduction
- c. Radiation

Conduction is the main contributor to the heat transfer. The heat energy transferred through the area at which the vial comes in contact with the shelf. It depends on the vial types used. It reduces in well plated or moulded vials usually. The amount of heat transferred is proportional to the temperature difference between the cold vial and warm shelf. The driving force in conduction is the temperature gradient between different solids.

Conduction can be explained by Fourier's law;

$$dQdt = A\lambda dTdz$$

Where,

$$dQdt = \text{Heat flow}$$

A = Area of surface

Λ = Thermal conductivity of material

dT = Temperature gradient across the thickness of the material

Radiation heat transfer takes place between two surfaces with different temperatures i.e. the cold vial and the shelf, the shelf, as well as the door of chamber. The warmer surface radiates electromagnetic energy which is absorbed on the colder surface. Stefan Boltzmann Equation describes radiative heat transfer;

$$dQrdt = A_v \epsilon \sigma T_2^4 - T_1^4$$

Where,

dQrdt = amount of energy per transmitted radiation

A_v = Vial area (top or bottom)

ϵ = effective emissivity for exchange of radiation (between 0 and 1)

σ = Boltzmann constant

$T_2 - T_1$ = difference between temperature of two surfaces to 4th power.

The effective emissivity is an important parameter for the surface materials used in the construction of freeze dryer. Acrylic glass shows high emissivity (0.95) while radiation of polished stainless steel is less (0.4). This difference should consider in lyophilization at the time of transfer and scale-up of lyophilization cycles between freeze dryers with radiation characteristics.

2. Mass transfer

The transfer of water vapour from the product to condenser is determined by several resistances to vapour flow that limit the flow rate. The most important factor is the resistance of the already dried layer to mass transfer, the so called product resistance (R_p). The water

vapour which sublimates at sublimation front needs to be transferred through a network of small pores in the dried product. The pores are created by the removal of ice by sublimation. R_p value depends upon the thickness of already dried cake layer, and change during the course of drying process.

In modelling, the product can be thought of a porous solid, with a Knudsen flow. The stopper can be modelled as a solid with transition flow through small tubes. The chamber can be modelled as a gas with viscous flow. The resistance associated with the product, R_p depends on the area of the product, A_p . This really become moving boundary problem, as R_p increases with time as the ice moves out of the product cake and must be solved through numerical methods.

Coupling of heat and mass transfer

The amount of heat produced is in equilibrium with the amount of heat removed in the sublimation of ice during the steady state. During the freeze drying heat and mass transfer are coupled can be described by;

$$dQdt = dmdt \cdot \Delta H_S + m_s \cdot c_v dTdt$$

$dQdt$ = flow of heat to product

$dmdt$ = removal mass by sublimation

ΔH_S = Temperature dependent heat of sublimation of ice

m_s = sample mass

c_v = specific heat of sample

$dTdt$ = change of product temperature

The first term indicates the rate of heat removal by sublimation and the second term signifies the rate of heat removal through a change in heat product temperature which happens mainly during early stages of primary drying. Since second term is usually small when compared to first term, heat transfer during steady state primary drying can be explained by simplified equation;

$$dQdt = dmdt \cdot \Delta H_S$$

This gives the conclusion, all heat introduced into the product is used to convert the ice to water vapour by **Pre-freezing**

In lyophilization method and final temperature affect ability to successfully freeze dry the material.¹¹ In lyophilization freezing step mainly affected by cooling rate. Rapid cooling rate mainly used for preserving stature to be examined in the microscopically but product is more difficult to freeze dry. Slow cooling rate lead to larger ice crystal but in the case of human or plant cell larger crystal can rupture and product is less restriction channels in the matrix to freeze dry.¹² Product can be freeze by two ways. Product consists of primarily of water, solvent material dissolved/ material suspended in the water or solute. Most sample are eutectics which freeze at lower temperature than surrounding water. In pre freezing step on cooling pocket are formed, ice contain pockets in which solute is present and have

sublimation, and the product temperature is assumed to remain constant.

DEVELOPMENTAL PROCEDURE OF LYOPHILIZED INJECTION

The lyophilization or freeze drying process involves three steps⁹;

a. Freezing

This step involves the freezing of water molecule and the dissolved component remains in the remaining freeze-concentrate which is in residual liquid form. When all the eutectic mixture frozen, then only the solution is said to be properly frozen and this temperature is called as eutectic temperature.

b. Primary Drying

In this step, the frozen ice get sublimed and dry, structurally intact product is obtained. This is the most time consuming step in this process. The chamber pressure and the shelf temperature adjustment gives optimized product.

c. Secondary Drying

After primary drying all the ice has sublimed but the residual moisture content still remains in the product. The continued drying is necessary to reduce the remaining water content to an optimum level.

Pre-treatment process

Fresh raw material

Washing

Cutting and shaping

Treatment to prevent quality change to flavour

Freeze-drying process

Refrigeration

Vacuum dehydration

Finishing

After treatment process

Selection and inspection

Packaging

Reconstruction process

Rehydration

Steps in freeze drying of herbal material

lower freezing temperature than water. Product seems like frozen but it's not completely frozen until all the solute in the suspension is frozen.¹³ Only when all of eutectic mixture is frozen then suspension properly frozen, this is called the eutectic temperature.¹⁴ Pre freezing is done below eutectic temperature before freezing step because small pockets of unfrozen material remaining in the product expand and compromise the structure stability of the freeze dried product. Second way the product that undergoes glass formation during freeze drying process. The entire suspension becomes increasing viscous as the temperature lower. Finally the product freezes at the glass transition point forming a viscous solid. This type of product is extremely difficult to freeze dry.¹⁵⁻²⁰

Freezing

While simple in concept, the freezing step is presumably the most complex step in lyophilization.²¹ As water freezes the dissolved components in the formulation remain in the residual liquid, a phase termed the freeze-concentrate. At the point of maximal ice formation, the freeze concentrate solidifies between the ice crystals that make up the lattice²². During primary drying, the crystalline ice formed during freezing is removed by sublimation. Therefore, the chamber pressure is reduced well below the vapour pressure of ice, and the shelf temperature is raised to supply the heat removed by ice sublimation.²³

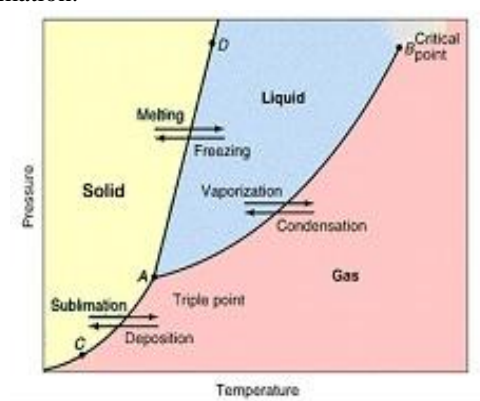


Figure 1: Phase diagram of water - Ice- Vapor system^{14, 24}

From this phase diagram of water, most products are frozen well below their eutectic point/glass transition point (A). Temperature is raised to just below this critical temperature (B). No matter what type of freeze drying system is used condition must be created to encourage the free flow of water molecule. Therefore vacuum pump is an essential component of a freeze drying system and is used to lower the pressure (C). The molecules have a natural affinity to move towards the collector chamber because its vapour pressure is lower than that of the product. Therefore the collector temperature (D) must be significantly lower than the product temperature.^{25,9}

So freezing can be defined as it is a process when ice crystallization occurs from super cold water.²⁶ In simple, in freezing process first Collision of solution that will lead to "nucleation" (nucleation is a process in which small nuclei is formed in solution or saturated solution).²⁷ The number of ice nuclei formed, the rate of ice growth, and the ice crystal's size depend on the degree of super cooling.^{28,29} That will lead to Ice crystals begin to grow at a certain rate, resulting in freeze-concentration of the solution, a process that can result in both crystalline and amorphous solids, or in mixtures of amorphous & crystalline. The freezing rate of a The phase diagram of pure water indicates that sublimation of water ice can occur only if the vapour pressure and temperature are below those of the triple point of water - i.e., below 611.73 Pa and 0.01°C, respectively.

formulation is not necessarily related to its cooling rate³⁰. Because the cooling rate is defined as the rate at which a solution is cooled & the freezing rate is the rate of post nucleation ice crystal growth, which is largely determined by the amount of super cooling prior to nucleation^{31,9}.

During slow freezing the nuclei have time to grow and the solution in between the ice crystals becomes increasingly concentrated. During quick freezing only small crystals can grow and the remaining solution can become so viscous that the water molecules cannot diffuse to the crystals and they become part of the solidified liquid (glass) between the ice crystals⁹.

• Primary drying

Primary drying is also known as main drying because in this phase of lyophilisation sublimation occurs. Sublimation occurs when a frozen solvent passes to gaseous phase without passing through liquid phase³². The ice crystals grow extremely uniformly using a special freezing method. The ice sublimates and the remaining solids show their original structure after freezing. During sublimation the temperature of the ice at the sublimation front (T_{ice}) has to be kept well below the collapse temperature (T_c)⁹. The end of the sublimation phase corresponds to the decrease in the moisture sensor signal down to a low constant value³³.

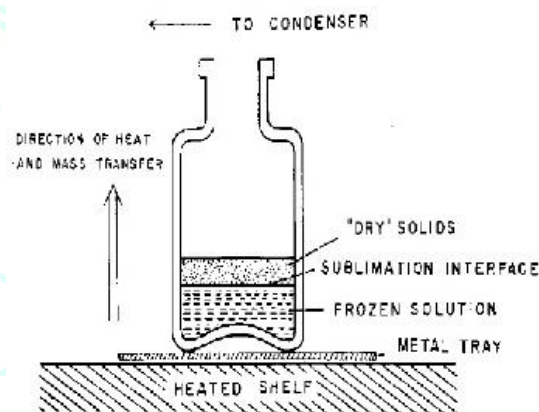


Figure 2: Vial during Primary Drying

Heat supply and vapour transport to the condenser are most important during primary drying. That's why the operation pressure is a very effective tool to control T_{ice} , if the shelf temperature is kept constant and the condenser temperature is always below a maximum, which depends on the water vapour pressure in the chamber and the design of the plant. Sublimation is the direct transition from solid state to gaseous state without melting. Sublimation occurs at a definite range of temperatures and pressures, depending on the substance in question.³⁴

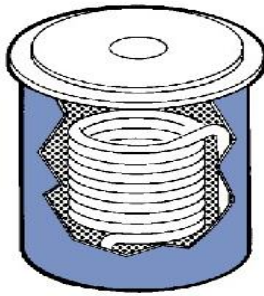


Figure 3: The collecting system acts as a cold trap to collect

In the end of sublimation process most of the water which is present in the form of moisture removed from formulation. In lyophilizer, vapour is formed after sublimation process in lyophilization chamber goes to condenser. Condenser continuously remove it.^{35,36} At the end of MD the ice is mostly sublimed and the measured T_{ice} decreases below the standard deviation of T_{ice} during MD³⁷. This effect can be used to change automatically from main to secondary drying (SD), e.g. if the measured T_{ice} becomes 2-3⁰C smaller than the average during MD.⁹

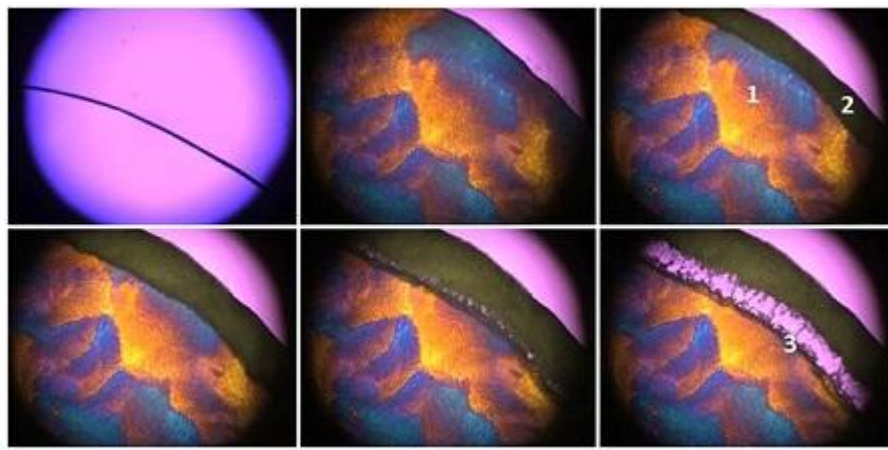


Figure 4: Freeze Drying Microscopy³⁸

Freeze Drying Microscopy^{38, 39}

Freeze drying microscopy is a method established in 1960s as a technique to determine critical parameters such as collapse temperatures. Besides the determination of collapse/eutectic temperature determination, nowadays it is used for identification of crystallization phenomena.

The knowledge of collapse behavior will be helpful in;

- Optimizing existing processes
- Developing a formulation for freeze drying.
- Developing a new cycle
- Scaling up

Eutectic Temp and Glass Transition Temperature

During freezing, ice crystals start separating out until the solution becomes maximally concentrated. On further cooling, phase separation of the solute and ice takes place. If the solute separates out in crystalline form, it is known as the eutectic temperature. In contrast, if an amorphous form is formed, the temperature is referred to as the glass transition temperature (Tg). Collapse temperature of esomeprazole sodium for injection 40mg was found to be -19.0⁰C⁴⁰

Table 1: Glass Transition Temperature and Collapse Temperature of Various excipients

| Excipients Name | Glass transition temp (Tg) | Collapse Temp (Tc) |
|-----------------|----------------------------|--------------------|
| Sucrose | -32,-35 | -34,-32 |
| Lactose | -28 | -31,-32 |
| Trehalose | -27,-29 | -29.5,-34 |
| Mannitol | -35,-28 | -1.0 |
| Sorbitol | -46 | -45 |
| Glucose | -43 | -40 |
| Raffinose | -27 | -26 |
| Glycine | -62 | -60 |
| Histidine | -33 | -35 |
| PVP (K40) | -20 | -23 |

Table 2: Eutectic temperatures for aqueous solutions of various compounds

| Compounds | Temperature in ⁰ C |
|------------------|-------------------------------|
| Citric acid | -12.2 ⁰ C |
| Glycine | -3.5 ⁰ C |
| Mannitol | -1 ⁰ C |
| Sodium acetate | -18 ⁰ C |
| Sodium carbonate | -18 ⁰ C |
| Sodium chloride | -21.5 ⁰ C |

Table 3: Glass transition temperature of various compounds

| Compounds | Temperature in °C |
|----------------------|-------------------|
| Dextran | -9°C |
| Fructose | -48°C |
| Glucose | -40to43°C |
| Sucrose | -32 to 34°C |
| Maltose | -32°C |
| Trehalose | -29.5°C |
| Sorbitol | -45 to 51°C |
| Lactose | -32°C |
| Ovalbumin | -10°C |
| Gelatine | -8 to 10°C |
| Polyvinylpyrrolidone | -23 to 24°C |
| Methylcellulose | -9°C |

Determination of end point of primary drying⁴¹

The longest and most complex part of the lyophilization process is primary drying stage. Therefore, automatic detection of end point of primary drying speeds up the process. In primary drying step, all unbound water is removed from the product.

One of the following techniques is used to optimize the primary drying process;

1) Product temperature end of primary drying set point

Frozen product will have a lower temperature than the temperature controlled shelf. We can assume that, when the shelf temperature and product temperature is same and the temperature reaches above 0°C there will be no ice. So, the product reaches the end point of primary drying.

2) Capacitance manometer differential test (capacitance manometer is required)

The pirani vacuum gauge measures relative vacuum and responds to the vapour present in the freeze dryer. The capacitance manometer indicates the absolute vacuum and is not affected by vapour pressure. The primary drying considered of completed when two gauges reads within the predetermined limit of reading.

3) Dew point via moisture sensor (moisture sensor is required)

To determine residual moisture content of the product, a moisture sensor may used. Moisture sensor is recorder in dew point (deg C). It can determine presence of liquid or ice in an amount less than 1%. A sharp decrease in dew point gives the indication of change of the ice to vapour at the end point of primary drying stage.

4) Barometric pressure rise (isolation valve is required)

Barometric pressure rise happens when the ice undergo sublimation and convert to vapour. When freeze drying chamber is isolated from the condenser and vacuum pump, the vapour pressure leads to a rise in vacuum.

When ice is present in the chamber, pressure will rise faster than without ice in the chamber and this indicates that the process not yet reached the end point. The pressure rise slows down when less ice presents in the chamber. The acceptable range of pressure rise to determine the end point of primary drying is less 6mT in 30 seconds in 3 or more readings in an hour.

• Secondary drying⁴²

After primary freeze-drying is complete, and all ice has sublimed, bound moisture is still present in the product. The product appears dry, but the residual moisture content may be as high as 7-8% continued drying is necessary at warmer temperature to reduce the residual moisture content to optimum values. This process is called 'Isothermal Desorption' as the bound water is desorbed from the product. Secondary drying carried out at high vacuum and moderate temperature (20–60°C). The dryer loses shelf control for 30 minutes during secondary drying as a result of a brief power outage. This results in the shelf temperature being maintained at 5°C cooler than the set point of 25°C. Secondary drying during lyophilization is intended to desorb bound water until the target residual moisture content specific for the product is achieved (typically < 1% w/w). It is also understood that during this phase of drying, the drying temperature is the more critical determinant of final moisture content over drying time.⁴² Hence, the main focus was on understanding the impact of the slightly lower cooling temperature on the final moisture content of the product.

Lyophilization of excipient

The design of a lyophilized formulation is dependent on the requirement of the Active Pharmaceutical ingredient and intended route of administration. A formulation may consist of one or more excipient that performs one or more function. Excipient may be characterized as buffer and pH adjusters, bulking agent, stabilizers and tonicity modifiers.

STERILIZATION OF PARENTERALS

After preparation of parenteral dosage form, it should be filled and sealed properly. The terminal sterilization is the main concern in parenterals. Within short time of filling and sealing, it should be properly sterilized usually by thermal process. Whenever high temperature affects the stability, we consider radiation sterilization. Heat labile products should be sterilized by non-thermal method, usually by filtration using bacteria retaining filters. All operations should carry out simultaneously in aseptic conditions to avoid the contamination of sterile product.

Dry-heat sterilization is applied for the products that require long heating period which is not get adversely affected by high temperature. This method is used for the sterilization of glasswares and metal wares. After sterilization, the equipment should be sterile, dry and pyrogens free.

Saturated steam under pressure (autoclaving) is used for the liquids or substances where the steam can penetrate into it. This is the most effective method for sterilization and most widely used.

PACKAGING OF PARENTRAL PRODUCT

43,44

The packaging of the parenteral products maintains sterility throughout the self-life of the product. Small volume parenteral has been package in ampoules which are heat stable after filling. Because of the inherent variability in the sealing process, product package in the ampoules must be 100 percent integrated testing after sealing, by dye integrity test The use of ampoules for new product is now diminishing, partly because of the

desire to avoid exposing medical personnel to injury on opening. This has led to increase in the use of glass vial sealed with rubber stopper for the packing of the small volume parenteral. When the vials or ampoules are used the glass quantity must be type I neutral.

Containers⁴⁴

Containers are defined as “that which holds the products and is or may be indirect contact with the products.” All containers for sterile preparations must be sterile, free of both particulate matter and pyrogens. These containers should not interact physically or –chemically with formulations to alter their required strength, quality, or purity. Chemical and physical characteristic are given primary consideration in the selection of a protective container. Mainly Glass container has been used for sterile products. Plastic containers are used for commercial ophthalmic preparation and intravenous solution.

A) Glass Containers

Glass is the most popular material for sterile preparation containers. Glass is composed principally of the silicon dioxide tetrahedron, modified physic chemical by such oxide as that sodium, potassium, calcium, magnesium, aluminum, boron, iron. The two general type of glass are soda-lime and borosilicate. The glass that is most resistant chemically is composed almost entirely of silicon dioxide, but it is relatively brittle and can only be melted and molded at high temperature. The USP provides the powder glass and the water attack tests for evaluating chemical resistant of the glass. The test results are measured of the amount of alkaline constituents leached from the glass by purified water under controlled elevated temperature condition.

Table 4: Different Type of Glass

| Type | General Description | General Use |
|------------|-------------------------------------|---|
| I | Highly resistant borosilicate Glass | Buffered and un-buffered aqueous solution, All other uses |
| II | Treated soda-lime Glass | Buffered aqueous solution with pH 7.0, Dry powder & oleaginous solutions. |
| III | Soda-lime Glass | Dry powder, oleaginous solutions. |
| NP | General purpose soda lime glass | Not for Parenterals, for tablets, oral solutions and suspension, ointment and other liquid. |

The greatest chemical resistant is provided by Type I Glass and least by non-parenteral glass. Type I glass is preferred for most sterile products, but type II and type III maybe used when product has a non-aqueous vehicle or the period of contact with the aqueous vehicle. The protection of the light sensitive product from the degradation effect of ultra violet rays may be an important physical characteristic of a glass container. Ultra violet rays can be completely filtered out by use of amber colored glass. Glass container should have sufficient physical strength to withstand the high pressure differentials that develop during autoclaving and that occurs during processing, shipping and storage.

B) Plastic Container

Plastic polymers can be used as sterile preparation containers but present three problems:

1. Permeation of vapors and other molecules in either direction through the container.
2. Leaching of constituents from the plastic into the preparation.
3. Absorption of drug molecules onto the plastic.

Plastics must meet USP specifications for biological reactivity and physiochemical. Most plastic containers do not permit ready inspection of their contents because

they are unclear. Most plastics also melt under heat

Closures

Rubber closures are used to seal the opening of cartridges, vials, and bottles, providing a material soft and elastic enough to permit entry and withdraw of a hypodermic needle without loss of the integrity of the sealed product. Rubber closures must be rendered sterile, free from pyrogens and surface particles. To meet these specifications, multiple washings and autoclaving are required. An autoclave heats sterilizing solutions above their boiling point to sterilize medical instruments. Closures are made of natural, neoprene, or butyl rubber. Thus, the rubber sealing of a vial or the plug in a syringe is a complex material that can interact with the ingredients of a formula.

CONCLUSION

Nowadays injectable dosage forms explore much more than other dosage forms because of more bioavailability,

sterilization.

patient compliance in geriatric and bed ridden patients and for fastest delivery of drugs to site of action.

Drugs which are formulating as injectable dosage form which have lower stability in liquid form subject to lyophilization. Lyophilization is the technique of choice over than other drying techniques to improve the stability of injection by avoiding the moisture content. The lyophilized injection gave a stable and therapeutically effective formulation which provides extended shelf life. Based on the drug characteristics, lyophilization technique was adopted to improve the cake characteristics of the drug molecule.

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