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Development of Stable Injectable Formulation by Freeze Drying Technique

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Abstract

Drug stability is a significant problem that affects drug quality. Freeze drying is one of the techniques that can be used to develop stable injectable-based drugs. This paper presents a new technique for developing regular injectable-based drugs by a freeze-drying process with the potential for various applications in bioengineering and the pharmaceutical industry. This review aims to improve the current injectable systems from unstable to stable by freeze drying technique. Injectable systems are dangerous, which leads to the degradation of the drug. The freeze-drying process can be used for sound injectable systems. Characteristics of proteins and peptides are the primary concern of the pharmaceutical industry. Freeze drying provides a new, safe, and effective way to preserve these substances without refrigeration or freezing. In the pharmaceutical industry, many efforts have been made to improve current protein formulations for injection. A new technique called freeze drying is emerging as a potential solution. This paper will explore the characteristics of freeze-drying and its possibilities for developing stable injectable drugs in more detail. Especially complex protein-based drugs present significant challenges to manufacturers because their stability is low, and they often have harsh conditions that need to be stored - such as being kept frozen or cooled on ice at all times.

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INTRODUCTION

A stable injectable drug formulation is a form of medicine suitable for injection. It has a longer shelf life and is less likely to degrade. An injectable formulation may be preferred over other formulations because it can be administered quickly, does not require refrigeration, and can be injected deep into the body [1]. A stable injectable formulation is a drug formulation that is not exposed to the environment and remains durable for an extended period. The main idea behind this formulation is to provide an effective drug that does not degrade in the body. This section introduces readers to a stable injectable formulation, why it was developed, and how it works. The mechanism of action of the drug is through inhibition of the enzyme beta-secretase (BACE), which is involved in converting amyloid precursor protein (APP) into amyloid-β (Aβ). The freeze-drying technique successfully developed a stable injectable formulation of BACE inhibitor [2].

This technique involves the application of a liquid to the surface of a frozen material. The liquid is absorbed as it moves to regions where water molecules are more available. The capillary motion

is responsible for the uptake and distribution of fluid. The frozen material melts and starts to thaw from its edges. Freeze drying has been used for many years in laboratory settings but has recently been applied to drug development and manufacturing through formulation stability and dissolution properties. We use a technique called freeze drying to create a stable injectable formulation. Freeze drying is a technique in which we reduce the water content of a solution by exposing it to the cold temperature of liquid nitrogen; We should be able to use this formulation to progress our research and provide insight into how we can better address diseases such as diabetes and malaria. There is a high demand for stable injectable formulations to keep the quality of medications at an optimum level [3].

Aside from the efficacy challenge, the issue of formulation stability is becoming more and more relevant with time. It has been estimated that about 75% of all drugs are administered via injections to patients; hence, this concern is not without merit. Pharmaceutical stability testing is an essential function in the development of a new drug. A formulation is stable if it has the following three characteristics: it maintains its physical integrity; it can be stored under defined conditions; it exhibits no change in the content of active ingredient(s) or disintegrating agent(s) or dissolution-inhibiting agent(s), or appearance (physical and chemical), during storage under defined conditions. A stable injectable formulation is one of the goals of drug formulation. This can be achieved by using additives. Stability testing includes chemical, physical, biological, and microbiological tests used to evaluate a product's or formulation's performance over its duration in storage and use [4]. Several instrumental methods can be used to measure and monitor a pharmaceutical product's degradation and stability: Gas chromatography separates molecules in a stream of gas or vapor based on their ability to interact with an electric current. - Rotary vacuum evaporator: this instrument will extract volatile materials from solids such as powders, tablets, and capsules. - Fourier transform infrared spectroscopy is an analytical technique involving the interaction between infrared radiation and molecules. Many factors affect the stability of an injection formulation. Some of these factors are natural, while others can be manipulated by taking certain precautions. Various factors that affect the strength of an injection formulation include temperature, pressure, light, additives, and excipients. The more the formulation is subjected to these variables, the greater its instability [5].

When the formulation is unstable, it can lead to many issues. This can be due to several reasons, such as environmental conditions and the manufacturing process. There is a need for an effective and efficient formulation that can last long and also retain its qualities like clarity and color. Companies sometimes solve this problem by processing their formulations in nitrogen [6]. To maintain the stability of their product, they have been doing so with some level of regularity since this issue first arose decades ago. With the advancement in technology, drugs have changed significantly. A stable injectable formulation is a common way of administering medication to patients. This drug type has advantages over oral tablets and suspensions because it is more convenient for patients and caregivers. It also offers an opportunity to increase patient compliance with treatment by reducing the frequency of injections for some drugs.

Different Types of Injectables

Injectable fillers such as Restylane and Juvederm can smooth wrinkles and folds on the face, plump the lips, and fill out hollows in the cheeks. Acne scars and lines from previous surgeries can be diminished with injectables such as Radiesse and Sculptra. Some people also use injectables to treat age-related conditions, such as droopy eyelids or thinning hair. There are various ways to inject these substances into the skin: manually or with a needle [7].

Injectable fillers: Restores volume and corrects moderate to severe facial wrinkles. Botulinum Toxin: Used to improve muscle tone and reduce the appearance of lines. Lip injections: To give the lips a fuller or more voluminous look. Some of the most popular types of injectables for cosmetic purposes include Botox, Latisse, and Juvederm. They are all commonly used to help people improve how they look daily. Botox is a neurotoxin that blocks nerve impulses from reaching their destination by relaxing the facial muscles and smoothing out wrinkles. Latisse is an eyelash growth supplement that lengthens, thickens, and darkens eyelashes to make them more attractive or noticeable. Juvederm is a dermal filler that lasts at least one year after treatment, making it perfect for those who do not want to go through the appointment every month, like with fillers like Restylane or Voluma [8, 9].

Injectable preparations are th most commonly used medications. They are administered directly into the body by injection. Here is a list of injectable preparations prepared by the freeze-drying technique.

- Adrenaline (usually prescribed for low blood pressure)

- Atropine (used to treat intestinal and bronchial spasms)

- Botulinum toxin (also known as Botox; used to treat muscle spasms or wrinkles)

- Calcium chloride (used to correct calcium deficiencies in people with specific diseases)

- Chlorhexidine (used as an intravenous antibiotic, disinfectant, and antiseptic)

- Desmopressin acetate (also known as DDAVP; is used for treating bleeding disorders like von Willebrand disease [10].

Injectables are drugs administered by inserting a needle under the skin or into a vein. It is usually reserved for patients who have difficulty swallowing or have problems with other methods. Injectables can be divided into three categories: liquids, semisolids, and solid preparations. Solid preparations are made by freeze drying technique, coming in a vial with a plunger. They can be divided into two subsections: dry powders and lyophilized powders. Dry powders are made from already freeze-dried drugs, while lyophilized powders are freeze-dried drugs that have been dissolved in water before being freeze-dried again to get the desired consistency for injection. Injectables are preparations of various medications, vitamins, minerals, and other pharmaceuticals. They are manufactured using the freeze-drying technique to allow their reconstitution into liquid form. Different types of injectables can be found on the market. Suspensions are designed to give a high-volume dose in a short period. Slow-release injections consist of medications delivered very gradually over a long period. And finally, injections can also be given as an infusion or an intravenous injection in the hospital setting to provide immediate relief for pain or injury during surgery [11].

Freeze drying technique in developing stable injectables

Freeze drying is when an organic substance is dehydrated by exposure to a vacuum. This way, it retains the high concentration of the senses while lowering the volume. The process starts with an organic substance placed into a container and then frozen to below -50°C. The vessel that contains the substance is then sealed and lowered into its chamber, producing a vacuum condition. This way, water vapor in the air starts to boil off, leaving only concentrated protein or other nutrients behind. All other liquids are also removed during this process [12]. After the substance has finished dehydrating, it will turn into powder form and should be reconstituted before consuming again. Freeze drying technique is a mechanical process by which water molecules are frozen. The water is frozen, followed by Sublimation, where the ice crystals are transformed into vapor without melting. This technique helps in preserving food products.

Freeze drying is preserving food by keeping it frozen while reducing the water content. The basic steps are to wrap the food in foil, place it in an airtight container, leave it in a freezer for an extended time, and then put the package into a vacuum chamber. The vacuum removes any traces of air molecules and replaces them with nitrogen gas. This process removes all the moisture within the food, which lasts longer than traditional preservation methods like canning or freezing. This technique is used today for foods like meat, fruit, and vegetables because they require long-term storage without risk of product spoilage or bacterial contamination [13]. Freeze drying removes the water from a substance by freezing it and turning it into gas. This technique can be used for many things, especially for food preservation.

The first step of the process is to freeze the food. The second step is to lower the temperature enough so that water in the food converts to ice crystals rather than liquid water. After this, the air is blown over this frozen material until the ice becomes water vapor. Finally, this water vapor will be absorbed by a cooling coil or an airtight container and condensed back into liquid at room temperature. The freeze-drying technique results depend on what you are trying to do - dry out porous materials like vegetables or fruit and harden solids like meat or potatoes. Freeze drying is a low-temperature food preservation process developed in the 1940s to preserve animal feed. This technique is not often used on consumer foods but can create an exemplary method for storing food without preservatives and additives [14]. The only drawback of this technique is that you must ensure your freezer can handle the extra load and usage.

Freeze drying is a technique that uses cold temperatures to remove water from food. This technique takes ice crystals out of the food and causes it to shrink. Freezing is a preservation technique that food producers can use to extend the shelf life of their products. The process involves rapidly cooling food items, usually with a blast of liquid nitrogen, to bring them down to their freezing point. The technique is popular because it prevents the growth of bacteria and enzymes, which would cause decomposition and spoilage if left unchecked by removing water from these items. It also maintains a product's shape and texture because the food does not

shrink as much as it would otherwise [15]. This technique is widely used for food preservation and can be applied to other materials like pharmaceuticals, biological research samples, and skin cells. Freeze drying aims to draw all the moisture out of an object or material. The general process starts with freezing the thing until it becomes solid (usually at a very low temperature). The frozen object is placed in a vacuum chamber where air pressure drops extremely low. The sublimated water vapor then turns into ice crystals that sublime off the thing, leaving it dry.

Some drugs can be freeze-dried and reconstituted with a sterile water injection solution.

The Process:

The freeze-drying technique is a process that has been used for many years in pharmaceutical industries. It is used explicitly for developing stable injectables from non-hygroscopic drugs [16]. A general explanation of the process is as follows:

1) Drug is dissolved in an organic solvent, usually acetone or ethanol.

2) The solution obtained from step 1 is concentrated by evaporation of the organic solvent under a vacuum, followed by lyophilization.

3) Matrix material is then added to the dry drug powder and dissolved into sterile water to the injection solution

4) Steps 2 and 3 are repeated until all drugs have been processed.

5) Then injectable is prepared.

Freeze drying is when the product is frozen and then subjected to a vacuum to remove water and create a dried powder or crystal. This process usually involves three significant steps: freezing, primary drying, and secondary drying. The freezing step consists of lowering the temperature of the product to less than -40°C (-40°F) by using conventional refrigeration or deep-freeze technology [17]. The primary drying step is accomplished by removing most residual moisture from the frozen product at pressures below atmospheric pressure; this is often done with a vacuum pump. Secondary drying completes the process by removing any remaining water from around 2 to 8% at forces greater than atmospheric pressure.

There are two main ways of drying drugs: spray drying and freeze drying. Spray-drying involves pouring a liquid drug solution into hot air. In contrast, freeze-drying consists of using a vacuum to remove the water from the drug and achieve a very low temperature. Freeze-drying is an efficient and affordable but also complex process. It is mainly used for drugs that cannot be dried with other techniques, such as paper-based solutions or porous solids, such as proteins and vaccines. As it requires less energy than other forms of dehydration, it's more environmentally friendly too. Freeze drying is a technique where the liquid is frozen and then subjected to a vacuum to remove the ice crystals, which can cause syringes to break. The process of freeze-drying starts by cooling the liquid down to a temperature at which it becomes a solid (Figures 1 and 2). This can be done by submerging them in liquid nitrogen or placing them in a freezer. The freezing generates heat, which will cause pressure on the container and the solution inside. This high pressure will eventually burst through any weak points in the container and eject some water left inside as ice crystals. Afterward, refrigeration is unnecessary as it freezes at room temperature. Then there would be no need for expensive equipment like compressors and condensers – just vacuum pumps and heat exchangers (Figures 3, 4 and 5) [18].

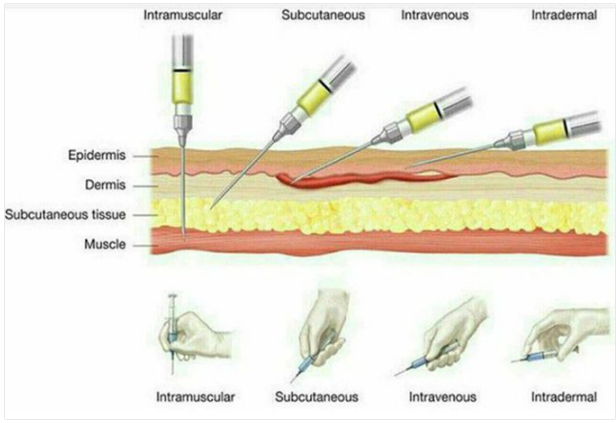

Figure 1: Typesof Injectables

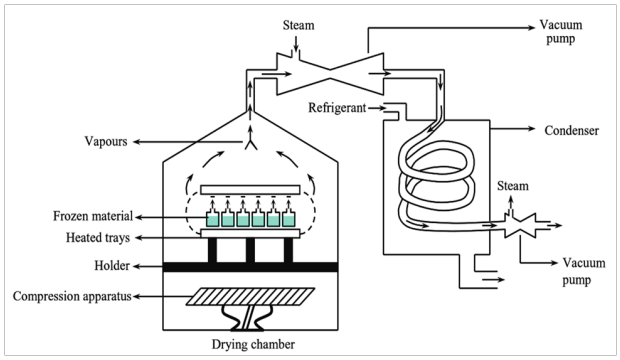

Figure 2: Schematic Diagram of Freeze Dryer

The freeze-drying technique is a technique that is used in developing stable injectables. The process involves the usage of liquid nitrogen, a drying machine, a vacuum pump, and molds. The liquid nitrogen is poured into the molds and then placed

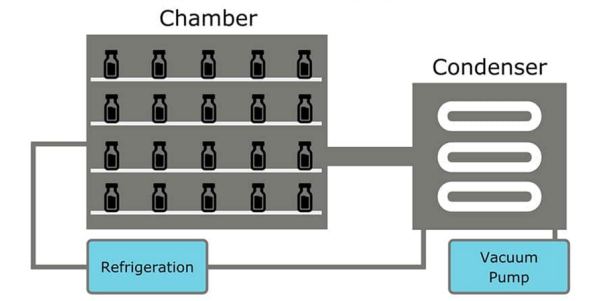

Figure 3: Diagram of a Lyophilizer

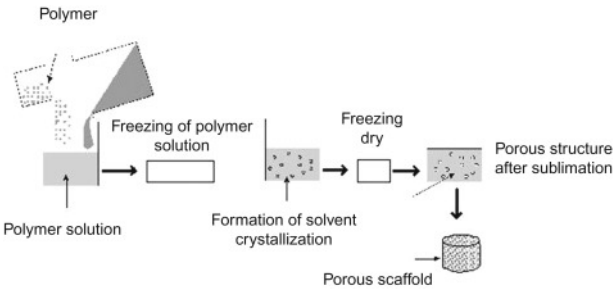

Figure 4: Processof Freeze Drying

in the freezing chamber, freeing all the water [19]. When this happens, it creates a vacuum to suck out any air inside the freeze-dried product. Afterward, the dryer drum will rotate to remove all moisture from the product, leading to dehydration. Finally, when this process has been completed successfully, three outcomes can happen to your freeze-dried product: it may be dehydrated enough for injection into patients without any need for preservatives or stabilizers; The freeze-drying technique is a process in which two liquids are frozen, and then, when their ice crystals are removed, the remaining liquid is left behind in the form of a dried product. This technique has been used to stabilize proteins or peptides. This process ensures that these proteins or peptides do not lose their structure because of water evaporation. This often occurs with injections because they can dry up when they come in contact with air.

Freeze drying technique is a process used to stabilize biological molecules, typically proteins or enzymes. It was first introduced in the 1990s by Dr. Yoshihisa Hagiwara, who discovered that this technique could be applied to developing stable injectable preparations. Freeze drying technique has been invented to address the stability and bioavailability of injection solutions [20]. The freeze-drying process involves removing water from a product by freezing it and lowering the temperature below its triple point, where the product will turn into solid ice without undergoing any change of state. It is reported that freeze-dried injection products are stable for up to 8 years. The problem with conventional drying methods is that they often result in a dry but not durable product, as the moisture content varies from batch to batch. Freeze drying technique has been around for quite some time; it is a process that involves freezing the product and subjecting it to vacuum conditions. The water in the product will be drawn off by Sublimation, leaving it dry but stable.

This removal of water content can potentially prolong its shelf life considerably. This can help avoid spoilage or any other form of degradation that may occur due to exposure to moisture over time. The freeze-drying technique is effective in preserving drugs in an easy-to-use format. Drugs are freeze-dried using a vacuum sealer to remove air. This process reduces the drug's temperature, preventing ice crystals from forming and breaking down the cell walls of the medicine [21]. This technique is not just for drugs but can also be used for food products that are too expensive or difficult to store. Freeze drying is a process that removes water from foods by lowering the temperature to the point where it sublimates out of the food. This is achieved by placing food in a freezer or using a freeze drier. It can be used to prepare foods for transport over long distances because freezing keeps food fresh for long periods [22].

Benefits of Using Freeze-Dried Injectables

It is important to note that freeze-dried injectables are not the same as injectable drugs. Freeze-dried injectables are not injected into the body or a vein but between tissues. Freeze-dried injectables are safe for patients with allergies because they do not have any residual solvents in them. Freeze-dried injectables can be stored at room temperature without refrigeration, which is an excellent benefit for hospitals. Using freeze-dried injectables is the next best thing to offer after the injectables. These are injectable drugs or medicines that are freeze-dried. It means these are not liquid and require reconstitution before use [23].

Some of the benefits of using freeze-dried injectables are:

1) They do not require refrigeration, so they can be used in remote locations where refrigeration is not available

2) They provide long shelf life, which is why hospitals prefer them

3) They can withstand various environmental pressures like fluctuations in temperature and humidity

4) Their reconstitution time is relatively short

5) Reconstitution time does not depend on whether it's heated or unheated water

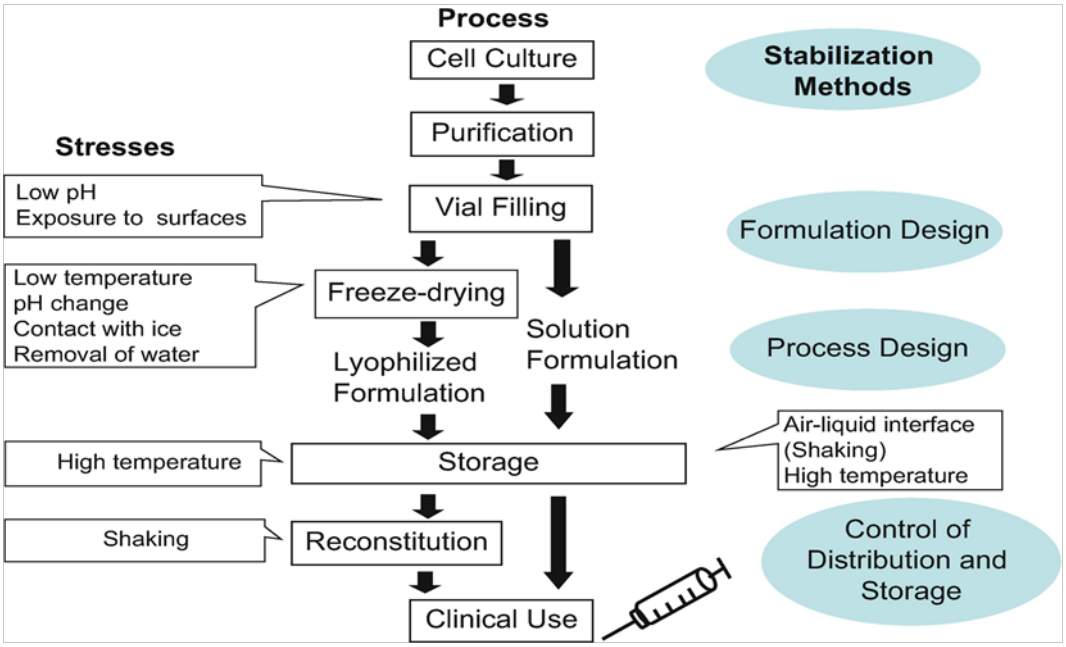

Figure 5: Freeze-drying technique

Freeze-dried injectables are the next generation of injectables. They are created by removing the water from injectable medications to make them easier to store and transport. The benefits of freeze-dried injectables are that they reduce the risk of bacterial infection, can be used with improper injection practices or in areas with limited resources, and have a long shelf life. One drawback is that it does not have an expiration date. Freeze-dried injectables offer several benefits that make them an ideal option for patients. First, freeze-drying the injectables eliminates the need for refrigeration and reduces the chances of bacterial growth. This makes storing and transporting the injections easy without fear of spoilage. Secondly, freeze-dried syringes are more accessible to manipulate than their traditional counterparts because they don't have any liquid inside and drip less on contact with the skin. And finally, freeze-dried injections often last longer than traditional ones because they don't deteriorate as quickly due to the lack of moisture [24].

Freeze-dried injectables are medications that have been freeze-dried to stop them from expiring.

Freeze-dried injections can offer several benefits for patients:

1) Preservatives are not needed, which means the medication is safer.

2) They are easy to store and can be used for up to two years.

3) They are easier on the environment since no chemical ingredients must be disposed of. The use of freeze-dried injectables has grown in popularity and is the latest trend in the medical industry. An injection is a method of introducing a substance into the body. The injection process typically involves drawing up a liquid medication from a vial using a needle, through an infusion set, or from an insulin pen and injecting it into the skin. Injections may be given into a muscle, intravenously (directly into a vein), or under the skin [25]. One of the benefits is that they offer quicker absorption rates to patients, which means temporary relief for them when they are experiencing acute pain. The next benefit is less preparation time required before administering it to them for pain relief. Freeze-dried injectables offer benefits that are appealing to patients. The injections are reliable, safe, and come in smaller quantities. The freeze-dried infusion can effectively treat many indications, including asthma, allergic rhinitis, and chronic obstructive pulmonary disease.

The freeze-dried injection process has been proven to reduce the risk of errors because it is easier to measure correct quantities. After all, making a new dose every time an injection is needed is unnecessary. Freeze-dried injectables are used in common treatments that include medication shots, blood transfusions, antibiotics, and more. Patients benefit from freeze-dried injections because they are easier to store and use than conventional injections. Freeze-dried injectables offer several benefits for patients; they are less likely to cause allergic reactions, take up less space in the body, and can be administered by medical professionals with minimal training. Freeze-dried injections are a form of medicine created by removing all the water from

a liquid and can be stored in a dry state indefinitely. Freeze-drying is done through the process known as lyophilization which removes all traces of water. The benefits of using freeze-dried injections are numerous. They offer cost savings, protection against contamination, no need for refrigeration, and it's easy to administer medicines [26].

CONCLUSION

The study showed that the freeze-drying technique was viable for making stable injectable formulations. The only difference with the freeze-drying approach is that the product is frozen and put in a vacuum chamber instead of spraying an aerosol of liquid nitrogen. Freeze drying is an attractive technique for manufacturing stable injectables because it can handle a large volume load and doesn't need time-consuming or expensive equipment. The pharmaceutical industry will have to wait for more practical development of the freeze-drying technique before they can start using it for developing injectables. It is now clear that this technique is not yet valuable enough for the industry to use, but with time, it will become a viable option. So, the freeze-drying process is widespread; it's been studied for at least the last 20 years. And what that technique does is that it removes water from a product by freezing it and then gradually reducing the temperature of that frozen block of development, which will eventually lead to ice crystals forming around the outside. This study found how to produce stable injectables with a high insulin dose using the freeze-drying technique. A new technique has been developed to produce stable injectables with a year's shelf life. Creating a stable injectable drug formulation is an important step forward in the pharmaceutical industry. The most popular technique for developing such formulations is freeze drying, which also has disadvantages. Presented here is a new technique that offers an alternative to this traditional strategy and some advantages. This conclusion summarizes the development of stable injectables by freeze drying technique and highlights the benefits and limitations of this technique. The decision provides an overview of the freeze-drying process and its development. It explains how easy it can be to store drugs in liquid form, but when they are solid, you need much more security, such as refrigeration or freezer storage. This technique also provides a much cheaper way for pharmaceutical companies to create liquid-based drugs, which can then be injected into their patients without any loss in potency. It concludes that while this technique has some limitations, it is a promising opportunity for many different areas in the healthcare industry because it could be a better solution than liquid-based injections or pills.

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Conflict of Interest

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REFERENCES

[1] Sandeep Nema and Ronald J Brendel. Excipients and their role in approved injectable products: current usage and future directions. *PDA Journal of Pharmaceutical Science and Technology*, 65(3):287–332, 2011.

[2] Robertson. Regulatory issues with excipients. *International Journal of Pharmaceutics*, 187(2):273–276, 1999.

[3] F A Crowe, L M Hoekstra, and J H Crowe. Anhydrobiosis. *Annual Review of Physiology*, 54:579–599, 1992.

[4] W Townsend and P P Deluca. Use of Lyoprotectants in the Freeze-Drying of a Model Protein, Ribonuclease A. *Journal of Parenteral Science and Technology*, 42(6):190–199, 1988.

[5] Sampathkumar Richard L Remmele, William J Krishnan, and Callahan. Development of Stable Lyophilized Protein Drug Products. *Current Pharmaceutical Biotechnology*, 13(3):471–496, 2012.

[6] Ketan Amin, Rose-Marie Dannenfelser, Joseph Zielinski, and Barbara Wang. Lyophilization of polyethylene glycol mixtures. *Journal of Pharmaceutical Sciences*, 93(9):2244–2249, 2004.

[7] A P Mackenzie. The physicochemical basis of the freeze-drying process. *Developments in Biological Standardization*, 36:51–67, 1976.

[8] M Her and S L Nail. Measurement of glass transition temperatures of freeze-concentrated solutes by differential scanning calorimetry. *Pharmaceutical Research*, 11(1):54–59, 1994.

[9] B. Raja, K. Narendra Kumar Reddy, and P. Swetha. Formulation and evaluation of chitosan nanoparticles containing Zidovudine for the target delivery into the brain.

Indian Journal of Research in Pharmacy and Biotechnology, 5(2):134–139, 2017.

[10] A P Mackenzie. Basic principles of freeze drying for pharmaceuticals. *Bulletin of the Parenteral Drug Association*, 20(4):101–129, 1966.

[11] R J Bellows and C J King. Freeze drying of aqueous solutions: maximum allowable operating temperature. *Cryobiology*, 9(6):559–5561, 1972.

[12] A N E Y Shalaev and Kanev. Study of the solid-liquid state diagram of the water-glycine-sucrose system. *Cryobiology*, 31:374–382, 1994.

[13] Evgenyi Shalaev. The impact of buffer on processing and stability of freeze-dried dosage forms. *American Pharmaceutical Review*, 8(5):80–87, 2005.

[14] Nam Ah Jun Yeul Lim, Dae Gon Kim, Ki Hyun Lim, Du Hyung Kim, Seong Hoon Choi, and Jeong. Process cycle development of freeze drying for therapeutic proteins with stability evaluation. *Journal of Pharmaceutical Investigation*, 46(6):519–536, 2016.

[15] Samir Mitragotri, A Paul, Robert Burke, and Langer. Overcoming the challenges in administering biopharmaceuticals: Formulation and delivery strategies. *Nature Reviews. Drug Discovery*, 13(9):655–672, 2014.

[16] S Rambhatla, S Obert, C Luthra, and Bhugra. Cake shrinkage during freeze-drying: A combined experimental and theoretical study. *Pharmaceutical Development and Technology*, 10(1):33–40, 2005.

[17] Christina Haeuser, Pierre Goldbach, Joerg Huwyler, Wolfgang Friess, and Andrea Allmendinger. Imaging Techniques to Characterize Cake Appearance of Freeze-Dried Products. *Journal of Pharmaceutical Sciences*, 107(11):2810–2822, 2018.

[18] Sabine Ullrich, Stefan Seyferth, and Geoffrey Lee. Measurement of shrinkage and cracking in lyophilized amorphous cakes. Part I: Final product assessment. *Journal of Pharmaceutical Sciences*, 104(1):155–164, 2015.

[19] Richard Ahmad M Abdul-Fattah, Holger Oeschger, Isabelle Roehl, Martin Bauer Dauphin, Georg Worgull, Hanns-Christian Kallmeyer, and Mahler. Investigating factors leading to fogging of glass vials in lyophilized drug products. *European Journal of Pharmaceutics and Biopharmaceutics*, 85(2):314–326, 2013.

[20] Gustavo Barreto Melo, Celso De Souza Dias Junior, Mariana Reis Carvalho, Alexandre Lima Cardoso, Fabio Barreto Morais, Ana Carolina Migliorini Figueira, Acacio Alves Souza Lima Filho, Geoffrey Guy Emerson, and Mauricio Maia. Release of silicone oil droplets from syringes. *International Journal of Retina and Vitreous*, 5(1):4–9, 2019.

[21] K Bechtold-Peters, W Friess, H Nalenz, H C Mahler, J Matilainen, and S Funke. Silicone 31 Migration From Baked-on Silicone Layers. Particle Characterization in Placebo and Protein Solutions. *Journal of Pharmaceutical Sciences*, 105(12):3520–3531, 2016.

[22] Christina Haeuser, Pierre Goldbach, Joerg Huwyler, Wolfgang Friess, and Andrea Allmendinger. Impact of dextran on thermal properties, product quality attributes, and monoclonal antibody stability in freeze-dried formulations. *European Journal of Pharmaceutics and Biopharmaceutics*, 147:45–56, 2020.

[23] Ken-Ichi Izutsu. Applications of Freezing and Freeze-Drying in Pharmaceutical Formulations. *Advances in Experimental Medicine and Biology*, 1081:371–383, 2018.

[24] L Steven, Shan Nail, Suchart Jiang, Chongprasert, A Shawn, and Knopp. Fundamentals of freeze-drying. *Pharmaceutical Biotechnology*, 14:281–360, 2002.

[25] A Gatlin and S L Nail. Protein purification process engineering. Freeze drying: A practical overview. *Bioprocess Technology*, 18:317–67, 1994.

[26] L Roy and M J Pikal. Process control in freeze drying: an electronic moisture sensor determines the endpoint of Sublimation drying. *Journal of Parenteral Science and Technology*, 43(2):60–66, 1989.

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