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INNOVATIVE LYOPHILIZED DOSAGE FORM OF BCS CLASS II DRUGS

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ABSTRACT

The development of lyophilized medication delivery systems has received a lot of attention in the pharmaceutical industry. This review's objective is to give readers a thorough overview of recent revolutionary advances in the development and use of lyophilized medicine delivery systems. This article highlights some of the most recent advancements in a variety of pharmaceutical formulations for BCS Class II drugs. These include ophthalmic lyophilisate carrier system (OLCS), lyophilized orally disintegrating tablets, lyophilization of nanocapsule, lyophilized nasal inserts, and lyophilized nasal suppositories. These formulations can be used to deliver a specific dose of medication and achieve a controlled release of the active ingredient. Pharmaceutical firms are focusing on the development of extremely sophisticated and sophisticated delivery systems in order to solve or fulfill key problems such cumbersome self-injection medication administration methods, the risk of needlestick injuries, and others (lengthy dose preparation timings).

KEYWORDS: Lyophilization, ophthalmic, Long-term stability, BCS Class II.

INTRODUCTION

One of the finest ways to support the long-term stability of many pharmaceutical medicinal products is lyophilization. A method of dehydration (a process that removes water molecules/desiccation) used in the food and meat sectors, various chemical industries, pharmaceutical, and biotechnology industries is lyophilization, sometimes known as "freeze-drying." Through a complicated process called lyophilization, pharmaceutical and biopharmaceutical materials are made stable through freeze-drying. Sublimation, the primary drying process, and desorption work together to lower the product's water content to about 3% by weight during lyophilization (secondary drying process). Pharmaceutical items that have been lyophilized are usually injected, and equipment and processing are frequently done in a sterile setting.[1]

The principal steps in a typical lyophilization process include:

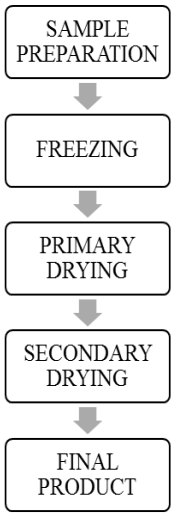

Figure 1: Steps involved in lyophilization.

The initial stage of lyophilization requires product preparation. This includes any process used to prepare the product before freezing. For example, a high vapour pressure solvent may be reduced, the product's surface area increased, the formulation revised (i.e., components added to promote stability and/or better processing) or the product concentrated. Pretreatment of a product is frequently required by cycle time or product quality criteria, or it is based on theoretical understanding of freeze-drying and its requirement.[2] Next step is freezing, so the sample must be completely frozen before pulling a vacuum and starting the drying procedure. Unfrozen food may expand outside of the container when exposed to a vacuum. [3] The majority of the water from the product is removed by sublimating all of the free ice crystals in a vacuum during the initial drying process. Additionally removed during first drying are organic solvents. The shelf temperature ranges from -30°C to -10°C, while the chamber pressure ranges from 40 to 400 Torr. A sizeable portion of water molecules that are attached to the product still remain in addition to the free ice that is sublimed during primary drying. During secondary drying, this is the water that is eliminated (desorbed). The product temperature can now be raised significantly without worrying about melting or collapsing because all of the free ice was removed during the initial drying process.[3] A product that has been freeze-dried should be sealed inside its container before being removed from the ultra-dry environment established at the end of the process. The formulation that has gone through this cycle typically contains less than 1% moisture, therefore when it comes into contact with an environment that contains moisture, the product will attempt to absorb moisture to the extent that it can.[4]

All solid actives that are heat-sensitive, chemically or biologically unstable, or when there is a possibility that a solution would interact negatively with the vial or package should be given lyophilization consideration. Many micro- and nanoparticulate systems have been created for effective drug delivery of proteins, peptides, or small compounds. Lyophilization has been a widely used method to get over such materials' physical and/or chemical instabilities in that situation. A viable remedy to this problem, particularly in the presence of non-aqueous co-solvents, is the creation of amorphous solid dispersions using lyophilization. This is because many novel chemical entities (NCEs) have poor solubility and bioavailability.[5]

There are many innovative lyophilized dosage forms available, this review comprises some of the innovative lyophilized dosage forms.

The Ophthalmic Lyophilisate Carrier System (Olcs): Development Of A Novel Dosage Form, Freeze-Drying Technique[6]

A novel dosage form for pharmacologically active chemicals or other substances that improve the structure of the tear film in the eye is the ocular lyophilisate carrier system (OLCS). A flexible hydrophobic carrier is joined to a drop of lyophilisate that contains the medicine and excipients that compose the majority of the drug and are water-soluble.

Figure 2: Administration of an ophthalmic lyophilisate carrier system (OLCS).[6]

Despite being widely used, traditional aqueous eye drops in multi-dose containers are a dosage form with many potential issues. Preservatives, which are known to harm the cornea and conjunctiva, must be added in order to retain their microbiological quality during usage. The pH is routinely changed for active substances that are hydrolyzing in order to provide sufficient stability at the expense of ideal physiologic tolerance. Low-viscosity eye drops drain quickly, especially if they are large, and the active components may be absorbed from the nasolacrimal duct and cause negative systemic effects. Many patients are unable to deliver the proper dosage in the proper location, hence it is common for the patient to administer more than one drop or to accidentally touch their cornea with the dropper tip, which may result in damage.

There have been numerous attempts to solve one or more of the issues related to the microbiological quality and simplicity of eye drop administration. New Ocular Delivery System (NODS), created by Smith & Nephew in 1996, was one of the most notable new products. In this device, the dose was supplied as an ophthalmic insert attached to a paper strip handle by a preformed soluble breakpoint. A single dose of the active ingredient is dissolved or dispersed in a drop of an aqueous solution of a hydrophilic polymer, which is freeze dried on a soft hydrophobic carrier membrane attached to a paper handle. This is the main concept behind the invention of the OLCS. Following administration, the lyophilisate attaches to the conjunctiva, is taken from its carrier by wiping across the lower eyelid, and dissolves in the tear fluid.

Both ease of administration and bioavailability depend on the degree of adhesion between the lyophilisate and the carrier as well as the structural firmness, or mechanical resistance of the lyophilisate to compression

and shearing. OLCS were created using standard laboratory freeze dryers, and both within and between batches, the adhesion force between lyophilisates and hydrophobic carriers varied. The lack of control over the freezing and drying processes as well as the uneven distribution of temperature profiles within the drying chambers were blamed for this. A tiny freeze dryer, which enables greater control of the freezing and drying conditions and shortens the manufacturing cycle, was created to achieve more uniform product features. The single unit's low cost, small size and isolation of the drying chamber from the main portion of the cooling system, which enables operation in either a laminar-flow workbench or an isolator, and ease of handling are notable qualities. [6]

Comparison of OLCS and conventional eye drops[6]

Table 1: Comparison of OLCS and conventional eye drops.

Sr. No.	Characteristics	OLCS	Eye Drops
1.	Preservative required	No	Yes
2.	pH adjustment to unphysiological values for the sake of stability	No	Frequently required
3.	Precision of dosage	Good	Poor
4.	Convenience of handling	Good	Poor
5.	Risk of injury upon administration	Absent	Present
6.	Ocular clearance and risk of systemic side effects	Low	High

Orally disintegrating olanzapine tablet[7]

The rapid-dissolving olanzapine formulation known as oral disintegrating olanzapine (ODO), which dissolves instantaneously in saliva, was created as a handy and adherence-improving substitute for the typical olanzapine-coated tablet (SOT). Within seconds, ODT starts to break down in the mouth, enabling its contents to be later digested with or without drink. The drug was dissolved in an aqueous solution of highly water-soluble carrier ingredients, including gelatin, glycine, and sorbitol, to create the ODT.

The gelatin was first fully soaked in water and produced as a 2% w/v solution in water. A magnetic stirrer was then used to agitate the hydrated gelatin until a clear solution was obtained. The gelatin solution was stirred while equal weights of glycine (0.886% w/v) and sorbitol (0.886% w/v) were added. The olanzapine powder (2.5% w/v) was then carefully weighed and mixed with the aqueous gelatin, glycine, and sorbitol solution. The resultant suspension was placed into each of the pockets of a tablet blister, yielding a 25mg dosage of olanzapine per tablet. The tablet blister packs were then placed in an ultra low freezer set at -40 °C and kept there for 24 hours. Each pack included 8 tablets. The frozen tablets were placed in a lyophiliser for 24 hours using a Freeze Dryer with a condenser temperature of -400°C and a pressure of 7×10-2 mbar, followed by a secondary drying at 25°C for 12 hours. Until the further experiment, the FDT were maintained at room temperature in a desiccator.

Regarding adherence, patient preference, and reduced nursing workload, ODO seems to have a lot of advantages versus SOT. When ODT is compared to SOT, ODT is not only better suited for difficult-to-treat, nonadherent patients but may also be an appropriate formulation for most individuals for whom olanzapine is the preferred antipsychotic due to its potential to enhance adherence and greater patient preference. Oro dispersible formulations have been discovered to have a significantly higher bioavailability than their conventional dose forms. Olanzapine is absorbed more quickly with ODO and reaches greater plasma concentrations sooner than with SOT. [7]

Lyophilization of nanocapsules

Aqueous suspension forms of nanoparticles, and more especially nanocapsules (NCPs), are typically produced. The main difficulty is the chemical and physical instability of such carriers in aqueous media. Their instabilities prevent them from being commercialised and do not guarantee long-term stability. It is necessary to immobilise the molecular mobility of the components of the nanocapsule system in order to overcome the chemical and physical instabilities. After drying, this immobilisation is possible to obtain. The hydrolysis of the polymer material producing the shell, the instability of the drug trapped inside, and the instability of thermosensitive ligands on the surface of NCPs are the key causes of their chemical instability. The aggregation and/or fusion of NCPs is frequently the cause of the physical instability. This is a significant barrier to the storage in aqueous medium. If only one of these instabilities is present, the drying procedure is therefore required to increase the stability of NCPs. The most popular procedure for creating pharmaceutical goods that are unstable and thermosensitive in aqueous medium is freeze drying, also known as lyophilization, in order to assure stability and long-term storage in the dried condition.

Although lyophilization is the best method, it may nevertheless result in a great deal of pressures that could cause the nanocapsules to become unstable. The formulation and subsequently the stability of dried NCPs may be impacted by the stresses, which might happen at various stages of lyophilization. For NCPs, the freezing and initial drying steps might be harsh. There is a phase separation between the development of ice and the cryo-concentration of the suspension in the interstis during the freezing stage of the nanocapsule suspension. The aggregation or fusing of NCPs may be caused by their excessive concentration. The removal of ice and unfrozen water during the drying process may potentially cause the particles to become unstable. Cryoprotectants

and lyoprotectants are two different forms of protectants that can be utilised to stop the instability of NCPs caused at the various stages. The term "cryoprotectants" refers to excipients whose main purpose is to safeguard the active ingredient and NCPs during the freezing process, as opposed to "lyoprotectants," which serve to stabilise them through both the freezing and drying processes. Most of the protectants employed in the lyophilization process are sugars, such as mannitol, trehalose, sucrose, glucose, or lactose. Only when utilised in relatively high quantities are sugars effective as cryoprotectants. Cryoprotectants frequently serve as lyoprotectants as well. Polymers can also serve as a protective layer. [8]

Lyophilization of olmesartan medoxomil nanocapsule[9]

Angiotensin II type 1 (AT1) receptor antagonist Olmesartan Medoxomil (OM) is used to treat hypertension. Due to the poor aqueous solubility of OM, only 26% of the supplied dose is absorbed orally from the gastrointestinal tract (GIT). The goal of the study is to determine whether the creation of lyophilized oily-core nanocapsules has improved the oral bioavailability of the antihypertensive medication Olmesartan Medoxomil (OM), which is poorly water soluble. Due to Brownian motion, colloidal nanocapsule dispersions are thought to be stable systems, although their stability may be compromised by polymer degradation, which may cause the active ingredient to migrate out of the core, as well as potential microbial contamination of the aqueous medium. The absence of water can make these systems more stable on a physical and chemical level. Freeze-drying or lyophilization is the method most frequently employed to transform liquids or suspensions into solids stable enough for distribution and storage.

The results showed that the lyophilized product could be easily inserted into a hard gelatin capsule shell and was stable at room temperature. The results also showed that the prepared OM-physical ONC's appearance and stability were enhanced by the addition of a cryoprotectant while the trapping effectiveness was maintained. Within one and a half hours of the trial, the lyophilized OM-ONC released 99.670.97%, but the pure OM powder HGC and the commercial tablet product only released 40.855.07% and 55.8312.2%, respectively. Better therapeutic antihypertensive action and fewer side effects than the conventional marketed tablet. [9]

Nasal inserts for drug delivery[10]

The nasal mucosa has been investigated as a viable administration route to obtain faster and higher levels of drug absorption while avoiding first-pass metabolism and ready accessibility because of its huge surface area, porous endothelium membrane, and high vascularization. Nasal bioadhesive dosage forms include hydrogels, inserts, micro- and nanoparticulate systems, and bioadhesive powders. Bioadhesive solid dosage forms, which allow for simple dosing and have a high potential for systemic distribution, hold the most potential among nasal inserts for extended drug delivery. The idea behind a nasal insert is the absorption of nasal fluid from the mucosa, followed by the development of a gel that, owing to its bioadhesive properties, attaches to the nasal mucosa and functions as a matrix for release control and prolonged drug delivery. There is no need to mechanically remove the insert once the medicine has been used up because the gel dissolves and/or moves towards the nasopharynx. Lyophilization can be used to create nasal inserts.[10]

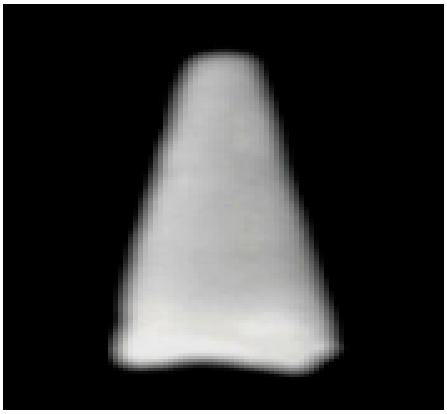

Figure 3: Shape of a freeze-dried nasal insert.[10]

Chlorpromazine, an antipsychotic, is being researched for nasal delivery systems with the following goals like to ensure systemic availability, useful for either acute treatment setting or long-term treatment of psychiatric illness, for patients who have difficulty swallowing tablets, extended drug permeation across nasal mucosa can be useful to reduce side effects, alter the pharmacokinetics of orally and parenterally administered drugs in a manner that can enhance their pharmacologic profiles. The preparation and characterisation of lyophilized nasal inserts that can deliver a specific dose of medication in the nasal cavity and achieve a controlled release of the active ingredient using hydration/diffusion mechanisms were the goals of this work. Chitosan/pectin polyelectrolyte complexes were utilised in this study to create nasal inserts that can extend residence time and control drug release by creating a gelled system in which the drug can diffuse. Mucoadhesive polymers can be employed to inhibit the quick clearance of the drug formulation. These polymers have unique biological characteristics such as mucoadhesivity, biocompatibility, and biodegradability. This innovative method expands the possibility of creating lyophilized formulations for nonparenteral purposes and is a practical means to lyophilize nonsterile items in their primary container.

Drug-loaded inserts (average diameter 5 mm, height 8 mm) were created by mixing complex/mannitol combinations with 100 L of chlorpromazine in aqueous solution (pH 5.5 phosphate buffer). The resulting suspensions were put into polypropylene microcentrifuge tubes, allowed to swell and remove air, and then were lyophilized to produce solid inserts that had a cone-like

shape. The release the drug is mainly in the following manner. The polymer in the inserts' structure absorbs mucin when they initially make contact with the highly vascularized nasal mucosa, quickly turns it into gel, and so provides a sustained emissions and/or controlled release profile.

All of the samples were distinguished by a sponge-like structure because nasal inserts were created by the process of freeze-drying, which involves the sublimation of frozen water leading to the development of holes or channels in the polymer. The nasal inserts' structure is dependent on the chitosan/pectin complexes' makeup, and the porous structure in particular has a tendency to vanish. It also favours increase water entry. The hydration of freeze-dried inserts results in gelling networks that can interact with mucus as a result of physical entanglement and secondary bonding after delivery into the nasal cavity and contact with the moist surface. This has strong mucoadhesive qualities. [11]

In-Situ lyophilization of vaginal suppository in unit dose applicator[12]

This invention relates to new products and methods that reduce the amount of product handling required during preparation and facilitate user handling and application. The product would need to be taken out of the packaging and put into an applicator for delivery by the customer. Handling vaginal suppositories excessively can be unhygienic and dangerous for the user because it can contaminate the suppository with bacteria that can subsequently be transferred into the vagina or another bodily cavity and lead to further infection. This invention relates to a method of producing vaginal suppositories or other suppository that minimises handling of the medication during production and use by filling unit dose cartridges with a liquid formulation containing the medication and lyophilizing (freeze-drying) the formulation inside the cartridges.

It explains how to make lyophilized or freeze-dried vaginal suppositories.

A plunger, barrel, and suppository are all parts of an in-situ lyophilized suppository product. The lyophilized cartridges that have been filled can then be packed and stored. When using the cartridges, the user need only take them out of the packaging, place the cartridge in the vagina, and manipulate it to release the suppository. In comparison to earlier vaginal suppository products, it represents improvements. This invention's lyophilized vaginal suppository often includes an active component, such as an antifungal drug or a spermicide. The preferred antifungal drug could be itraconazole, econazole, terconazole, or miconazole nitrate.

Prior to filling them with the liquid mixture, cartridges are placed into metal mesh. The plug is then placed into the cartridge before it is filled, acting as a basis to keep the full product inside the cartridge. Then do the freeze-drying or lyophilization process. [12]

CONCLUSION

In the freeze-dried solid state, chemical or physical degradation reactions are restrained or appropriately slowed down, increasing long-term stability. Formulations that have been lyophilized have good stability as well as easy handling during storage and transit. Pharmaceutical companies are focusing on the creation of increasingly advanced lyophilized drug delivery systems in an effort to address or solve major issues including the difficulty of administering medication via self-injection, the danger of needlestick injuries, and others (lengthy dose preparation timings). It is expected that the market for lyophilized pharmaceuticals will reach US$ 322.9 billion in 2018 and experience a CAGR of 7.1% during the following five years (2018–2026).

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