INTRODUCTION

1.0 LYOPHILIZATION DEVELOPMENT

Lyophilization (freeze-drying) is often used to prepare dry pharmaceutical formulations to achieve commercially viable shelf lives. Lyophilization is an effective manufacturing process to prevent hydrolysis in otherwise unstable injectable products. A key feature of the lyophilization process is the sublimation of water from an aqueous solution of the drug at temperatures typically below zero degrees Celsius under high vacuum. Since the operation is usually conducted with frozen solutions, chemical degradation is typically not an issue during the lyophilization process; which depending on the volume and composition of the solution which can take several hours or even days. For biological materials such as vaccines, lyophilization is often the only way to evaporate the solvent while maintaining their desired biological activity. Some lyophilized drug products (small molecules as well as vaccines) are furthermore unstable in the presence of oxygen. Storage of these lyophilisates under vacuum or under a blanket of inert gas often ensures adequate stability over the anticipated shelf-life of the product (Thanaset Senawong, et al (2008)).

1.1 PHARMACEUTICAL DEFINITION

The lyophilization process is defined as “A stabilizing process in which a substance is first frozen and then the quantity of the solvent (generally water) is reduced, first by sublimation (referred to as the primary drying process) and then desorption (known as the secondary drying process) to values that will no longer support biological activity or chemical reactions”

1.2 DESCRIPTION ABOUT LYOPHILIZATION PROCESS

The lyophilization, or freeze dry, cycle is the means by which a freeze dried product is produced. A typical freeze dry cycle is generally described in terms of three phases - freezing, primary drying and secondary drying. The freezing phase involves the immobilization of water-ice and freeze-concentration of the product solution. The primary drying phase involves removal of the water-ice by sublimation via application of high vacuum to the chamber and input of heat to the lyophilizer shelves. Secondary drying
describes removal of unfrozen water from the product matrix post-ice removal. Generally, the lyophilization cycle is described in terms of the parameters which set the conditions under which a product is lyophilized (e.g., shelf temperature and chamber pressure). Alternatively, the freeze dry cycle can be thought of as the thermal profile which the product undergoes during lyophilization to achieve a final dry powder. While in principle similar, the difference between these two descriptions of lyophilization cycle is the core of scale-up and process transfer.

With the end-point (target cake moisture after lyophilization) firmly established during drug development, the actual manufacture of lyophilized products typically involves:

- Filling of the vials with the aqueous drug and Excipient solution
- Loose capping of the vials with the stoppers
- Charging of the lyo chamber with the vials from step 2
- Performing the lyo cycle to the desired end-point
- Final capping of the vials under full vacuum or after the venting of lyo chamber with an inert gas to a desired internal vial pressure
- Removal of the vials from the lyo cabinet and further packaging

1.3 ADVANTAGES

Lyophilization has many advantages compared to other drying and preserving techniques.

- Lyophilization maintains drug product quality because the drug product remains at a temperature that is below the freezing-point during the process of sublimation; the use of lyophilization is particularly important when processing lactic bacteria, because these products are easily affected by heat.
- Drug products which are lyophilized can usually be stored without refrigeration, which results in a significant reduction of storage and transportation costs.
- Lyophilization greatly reduces weight, and this makes the products easier to transport. For example, many drug products contain as much as 90% water. These drug products are 10 times lighter after lyophilization.
Because they are porous, most freeze-dried drug products can be easily rehydrated. Lyophilization does not significantly reduce volume; therefore water quickly regains its place in the molecular structure of the drug product.

1.4 DISADVANTAGES

The principle disadvantages of lyophilization are:

- High capital cost of equipment (about three times more than other methods)
- High energy costs (2-3 times more than other methods)
- Long process time (typically 24 hour drying cycle)

Lyophilization should be used when the product meets one or more of the following criteria: unstable; heat liable; minimum particulates required; accurate dosing needed; quick; complete rehydration needed; high value. Some other less common applications of lyophilization are recovery of water-damaged books and manuscripts and preservation of archaeological specimens, tissue for spare-parts surgery, museum specimens for display such as plants and animals, and vegetable matter for research programs (Jennings, T. A.et, al, (1999)).

2.0 NOVEL EXCIPIENTS

We've all read about it: the US Food and Drug Administration approved 17 New Molecular Entities and 2 biologics in 2007, continuing the downward trend in drug approvals occurring over the last decade. The number of drug approvals in 2007 is the lowest number since 1983 and 68% lower than the number approved in 1996 (Hughes 2008). Analysts have suggested many potential explanations for this trend, from tightening safety standards at the Agency to increasing costs and complexity of clinical trials and a shift in emphasis at pharmaceutical manufacturers away from truly ground-breaking treatments.

One area that has not received much scrutiny is the lack of innovation in the area of pharmaceutical excipients. The choice of excipients can spell the commercial and scientific success or failure of each active pharmaceutical ingredient (API): an API which performs
unique and beneficial functions in biologic systems but cannot be formulated in a viable delivery system is essentially useless. Nevertheless, global excipient research and development are frozen in time, hamstrung by inconsistencies in the regulatory and safety framework which do not allow for approval of new excipients outside the context of a New Drug Application (NDA). Pharmaceutical manufacturers, wary of any additional risks to approval, are therefore reluctant to use new excipients in formulations under development, and excipient manufacturers are finding it difficult, if not impossible, to find customers for their innovative products (Jay Goldring, et, al, (2009).

2.1 DEFINITION BY USFDA & IPEC

In the US, "novel" excipients are defined in the guidance document, "Nonclinical Studies for the Safety Evaluation of New Excipients" (US FDA, 2005) as "any inactive ingredients that are intentionally added to therapeutic and diagnostic products, but that: (1) we believe are not intended to exert therapeutic effects at the intended dosage, although they may act to improve product delivery (e.g., enhance absorption or control release of the drug substance); and (2) are not fully qualified by existing safety data with respect to the currently proposed level of exposure, duration of exposure, or route of administration."

In practice, new excipients in the US are those not listed on FDA’s official list of approved excipients, the Inactive Ingredient Guide, posted on the FDA website at http://www.accessdata.fda.gov/scripts/cder/iig/index.cfm.

The International Pharmaceutical Excipients Council defines excipients as “substances, other than the active drug substances of finished dosage form, which have been appropriately evaluated for safety and are included in a drug delivery system to either aid the processing of the drug delivery system during its manufacture; protect; support; enhance stability, bioavailability, or patient acceptability; assist in product identification; or enhance any other attributes of the overall safety and effectiveness of the drug delivery system during storage or use”.
2.2 SIGNIFICANCE OF NOVEL EXCIPIENTS IN PHARMACEUTICAL INDUSTRY

Novel excipients could represent a needed source of innovation for the pharmaceutical industry. The current regulatory system is a substantial barrier to such innovation. Since most excipients are designed to be biologically inactive, removing this barrier could provide a potentially immediate, low-risk solution to the current shortage of new drug formulations. The current system of excipient approval, in which approval in the first drug application provides automatic approvals for subsequent applications for similar routes of administration, may serve only to add an unnecessary barrier to the development of drug formulations containing novel excipient.

The excipients used in pharmaceutical preparations are limited and from an academic point of view there is a clear requirement for new excipients (Jay Goldring, et, al (2009)).

2.3 REGULATORY ISSUES AND OFFICIAL GUIDES TO CHOICES OF EXCIPIENTS

For an excipient to be approved as a part of a formulation its inclusion has to be justified, the compatibility with the active ingredient shown, and the quality (or grade) will have to be either justified or shown to be sufficient to fulfil the requirements for the final product. Furthermore, the suggested amount of excipient must be shown to be sufficient for the intended function of the excipient. No official lists are readily available to guide on the amount, types and use of excipient. Nevertheless, the Federal Drug Agency (FDA) has made a database and an Inactive Ingredients Guide from 1996 publicly available, in which the use of various excipients in registered products for the different delivery pathways is listed. A similar list was available at one point on the European Medicines Agency (EMEA) site.

The introduction of excipients to a formulation requires thorough studies of the interaction between the specific excipient and the active ingredient or other excipients and of how stability is influenced. This requires extensive knowledge, especially if a new substance is being used. As a consequence, there is a tendency among pharmaceutical companies to use well-known excipients as a starting point for new protein formulations.
Several requirements must be fulfilled in order to introduce new substances as excipients in protein drug products. The excipient must be available from a reliable supplier and obtainable in the right quality with a controlled level of residual solvents, preferably of non-animal origin and produced according to GMP requirements. When new excipients are proposed, their prior use in either the food or the cosmetic industry for similar delivery pathways (e.g., dermal) may ease the application process. Excipients that are controlled by pharmacopoeial monographs are often preferred. However, even though an excipient may be of pharmaceutical grade it may previously have been used only in formulations for routes of administration other than that desired for the product under development (Matthews B, et, al, (2002)).

2.4 SAFETY, TOXICITY AND IMMUNOGENICITY OF EXCIPIENTS

In drug formulation, the safety of excipients is as important as the safety of the active product ingredient. For well-known excipients that have been recognized and used for a long time, the question of safety is mainly one of quality control of the products received from suppliers. For new excipients, thorough documentation is required including its safety, toxicity and immunogenicity by the EMEA and FDA.