Research and Reviews: Journal of Pharmaceutical Analysis

e-ISSN: 2320-0812
p-ISSN: 2347-2340

Review on Lyophilization of Anti-biotics

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Review Article

Received: 02/12/2016
Revised: 08/12/2016
Accepted: 14/08/2016

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Keywords: Lyophilization, Aniti-biotics, Dosage form

ABSTRACT

The process of Lyophilization is carried out in pharmaceutical solutions inorder to produce an acceptable and stable product has been a practice employed to manufacture many marketed injectable formulations. Lyophilization which is based on the principle of sublimation of ice is a process of removal of water by, conversion of ice directly from solid to vapour without passing through a liquid phase. It includes the processes like freezing, sublimation and desorption. The present marketed formulation is taking more amount of time to get lyophilized and is facing problem of cake integrity during transport and upon prolonged storage. So the present work is designed to formulate a lyophilized Piperacillin tazobactam powder for injection, with decreased lyophilization time, increased stability and make the product more economical. Thus, the important objective of this research is to formulate a stable lyophilized formulation with desired characteristics, by combining with different excipients

INTRODUCTION

Antibiotics

The greatest drugs of the 20th century to therapeutics are Anti-biotics. The drugs are designed in such a manner that they have the ability to inhibit/kill the infecting organism and there should not be any l effect on the recipient. Such type of action is known as chemotherapy. Chemotherapy is the treatment of disease by the use of chemical substances, especially the treatment of tumor by cytotoxic and other drugs. The basis of selective microbial toxicity is the action of the drug on a component of the cell wall or folate synthesis that is not found in the host. Waksman coined the word anti-biotic during 1942; Previously they were called lysins, bacteriolytic agents [1-5].

PRINCIPLES OF FREEZE DRYING

The process consists of three steps or processes:

- Freezing
- Sublimation
- Desorption

Freezing

Formulation is cooled during this stage. Pure crystalline ice forms from the liquid, thereby resulting in a freeze concentrate of the remainder of the liquid to a more viscous state. Ultimately this highly concentrated and viscous solution solidifies yielding a solid product. Small ice crystals produce pores with lower volume-surface area, thus resulting in lower diffusion and sublimation rates [5,6].

Primary drying

As the drying proceeds, thickness of the frozen layer decreases and the thickness of partially dried solid increases. The transfer of heat is generally done by conduction or radiation. Convection effect is negligible, due to low air density. After sublimation, vapour molecules get collected in the condenser. The condenser provides a surface for the water vapour to re-solidify on it. Condenser temperatures are typically below -500°C [7,8].

Secondary drying

e-ISSN: 2320-0812
p-ISSN: 2347-2340

During this process, traces of remaining water are removed. Bound moisture will be found in the product, even after all the ice has sublimed during primary drying. 7-8% of residual moisture may be present in the product, but the product appears dry. The bound water is desorbed from the product. The relatively small amount of bound water remaining in the matrix is removed by desorption. Temperature is increased more than that in primary drying. The temperature of the solid is raised to as high as 500°C to 600°C [9,10].

EXCIPIENTS In a LYOPHILIZED FORMULATION

Most freeze dried products contain several components in addition to active pharmaceutical ingredients (API). These additional components, known as excipients, are intended to serve a specific function, normally related to stability or process. They are as follows:

Bulking agents

Bulking agents are intended to be inert and improve product elegance and blow-out of product is prevented. The structured of lyophilized cake is important, since proper cake formation leads to proper pore formation, that provides the means for vapour to escape from the product during drying. (Ex: Mannitol, Lactose)

Buffering agents

Sodium hydroxide, Sodium bicarbonate.

Tonicity adjusters

Parenteral formulations must be isotonic with the blood plasma, so as to avoid damage to tissues. However, not all drugs at their recommended dosage are isotonic with blood, thus requiring the addition of a tonicity adjusting agent. (Ex: Sodium chloride, Glycine, Glycerol).

Surfactants

Generally surfactants are added to improve wetting and reconstitution behavior, and to stabilize proteins during freezing. Surfactants are generally added to low dose products to minimize losses due to surface adsorption (i.e. when the total amount of drug loss is a significant percentage of the drug in solution). (Ex: Polysorbate 80) [11-30].

PROCESS OVERVIEW

In freeze drying, solution is filled into vials; a special slotted rubber closure is inserted halfway into the vial, which allows escape of water vapour. Vials are placed on trays and transferred to freeze dryer. Trays of product are placed on shelves containing internal channels, allowing circulation of silicone oil. The solution is frozen by circulation of silicon oil through internal channels in shelf assembly. When the product is solidified sufficiently, the pressure in freeze-dry chamber is reduced. After this pressure is reached, heat is applied to the product by increasing the temperature of circulating fluid. As drying proceeds, a receding boundary can be observed in the vial as the thickness of the frozen layer decreases, and the thickness of partially dried solid increases. It happens due to direct sublimation of ice in the primary drying phase of lyophilization. The concentration gradient of water vapour between the drying front and condenser is the driving force for removal of water during lyophilization. After primary drying, additional drying is necessary to remove any water that did not freeze during the freeze process. This phase is required to remove water adsorbed to or trapped by the solid matrix. This phase is called secondary drying and consists of water removal by diffusion and desorption. When the product is sufficiently dry, vials are usually stoppered in place by hydraulic compression of shelf stack which pushes vials to fully inserted position.

DETERMINING DRYING ENDPOINTS

The drying boundary in vials moved to the bottom of the product reveals that no ice is visible in the product. As the heat input to the product is increased, evaporate cooling keeps the product temperature well below the temperature of its surrounding atmosphere. When the primary drying is complete, the product temperature rises to equal the temperature of its environment.

Drug Excipients Compatibility Study

Excipient compatibility study gives valuable information about potential incompatibilities between API and excipients [31-40]. Compatibility between API and excipients can be affected by many factors such as moisture content, physical form, particle size, morphology etc. The stressed storage conditions used to accelerate reactions between API and excipients are carefully selected such that, measurable changes occur in short time frame, while ensuring that such data remains applicable to ambient conditions. In the present study, compatibility of Piperacillin and Tazobactam with excipients like Sodium Bicarbonate, Mannitol, Lactose and Dextrose was studied for a period of one month. The drugs and excipients were taken in 1:2 (50 mg + 100 mg) ratio and loaded for stability studies at 25 ± 20°C/60 ± 5% RH and 40 ± 20°C/75 ± 5% RH accelerated temperatures and related humidity. The samples were analyzed for drug stability by HPLC method [41-50].

e-ISSN: 2320-0812
p-ISSN: 2347-2340

The drug is analyzed by HPLC by dissolving the contents with 10 ml of water for injection.

FORMULATION

Procedure

Required quantities of drugs and excipients are collected and weighed accurately. Water for injection (A) was freshly collected and the temperature is maintained at 12 ± 20°C. 10 ml of this WFI (from A) was taken in a separate beaker and to this 2 gm of Piperacillin was added slowly followed by 100 mg of Sodium Bicarbonate with constant stirring (B) [51-60]. In another beaker 5 ml of WFI (from A) was taken and to this 0.25 gm of Tazobactam was added slowly followed by 20 mg of Sodium Bicarbonate with constant stirring (C). This Tazobactam solution (C) is added to the above Piperacillin solution (B) [61-65]. To this required quantity of selected bulking agent was added. Final volume was made up to 20 ml with WFI (from A) and mixed properly until completely dissolved using a sonicator. pH was checked and adjusted with Sodium bicarbonate to 5.5-7.0 if required. 0.22 µ Millipore syringe filter is used to filter this solution. The solution is filled into vials. The vials are partially stoppered and loaded into trays of the lyophilizer. The lyophilization cycle was started and after the cycle is completed the vials are removed from the trays and are stored at suitable temperature for further analysis [65-75].

The bulking agents used are:

- Mannitol
- Lactose
- Dextrose

DEVELOPMENT of LYOPHILIZATION CYCLE

The solution is filled into vials. The vials are partially stoppered and loaded into trays of the lyophilizer. Different lyophilization cycles were tried to optimize the cycle which produces stable and uniform cake [76-82].

CONCLUSION

The present research work was designed to develop a lyophilized Piperacillin/Tazobactam powder for injection with improved stability and being more economical when compared to the present marketed formulation [83-90]. The marketed formulation has problem of stability upon prolonged storage and is also taking more time for the process of lyophilization to get completed. Therefore the present work was focused on overcoming the drawbacks associated with the present marketed formulation and to formulate a stable product that is found to be economical. To improve the stability and cake characteristics of the lyophilized formulation, three bulking agents were selected in different concentrations. Three different lyophilization cycles were carried out using different combinations of these excipients and drugs. From the results it was revealed that, lyophilization cycle 3 and formulation F2 with 5% mannitol produced good results as the formulation exhibited a good cake structure and evaluation factors were found to be with in the USP limits. From the results a conclusion can be reached that, the use of bulking agents produced stable injectable dosage form of Piperacillin tazobactam with improved cake structure and decreased lyophilization time [91-100].

SUMMARY

Piperacillin is an extended spectrum beta–lactam antibiotic of the ureidopenicillin class, useful in treating many gram positive and gram negative pathogens, including *Pseudomonas aeruginosa*. Tazobactam is a compound that inhibits the action of bacterial β-lactamases. It is combined with the Piperacillin. This combination is available as lyophilized powder for injection. Preformulation studies of the drugs were performed for their description, solubility, pH, water content, melting point, assay and the results were found to be within the limits. Compatibility of the drugs with excipients was determined. The drugs were formulated by using various excipients such as mannitol, lactose and dextrose in different concentrations and were lyophilized. A total of six formulations with different concentrations of excipients were prepared and were lyophilized using three different lyophilization cycles.

Finally it was concluded that lyophilization cycle 3 was the best process, with F2-5% mannitol being the best formulation passing all the tests. Hence, F2 with 5% mannitol was selected as the best formulation for the lyophilization of Piperacillin/Tazobactam combination.

e-ISSN: 2320-0812
p-ISSN: 2347-2340

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