CHAPTER I

INTRODUCTION

Pralidoxime chloride, 2-[(Hydroxyimino) methyl]-1-methylpyridinium chloride, 2-pyridine aldoxime methochloride, 2-PAM Chloride, is a cholinesterase reactivator (1,2). The pharmacological effect of pralidoxime is reactivation of cholinesterase, which has been recently inactivated by phosphorylation as the result of exposure to certain organophosphates. Pralidoxime removes the phosphoryl group from the active site of the inhibited enzyme by nucleophilic attack, regenerating active cholinesterase and forming an oxime complex. The therapeutic value is an antidote to poisoning by organophosphate agricultural chemicals, chemical warfare agent, nerve gas and drugs acting as cholinesterase inhibitors (3).

Pralidoxime chloride occurs as a white to pale yellow, crystalline powder and is freely soluble in water. Its chemical structure is a quaternary ammonium oxime.

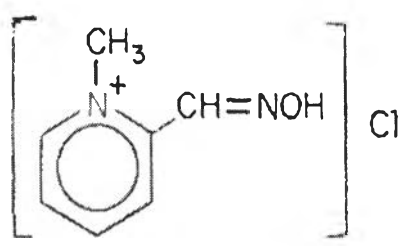

Figure 1 Structural formula of pralidoxime chloride

Pralidoxime chloride is less stable in solution but improved by buffering the solution to a pH value near 3(5). In different conditions of pH and temperature, pralidoxime chloride has been decomposed to a variety of products (6,7). The degradation products are 1-methyl-2(1H)-pyridinone, cyanide, ammonia, carbondioxide, 1-methylpyridinium salts.(8)

The preparation of pralidoxime chloride is a 1-gram sterile powder for injection. The freeze drying process or lyophilization should be optimized due to the fact that products currently on the market are not consistent in terms of its solid state stability, acceptable appearance and, as a result, the bioavailability. Freeze-drying is a process in which the solvent (usually water) is first frozen and then removed by sublimation in a vacuum environment. The technique has developed into a widely used method for the stabilization of otherwise easily degraded substance. There are several characteristics of the freeze drying process that make it desirable over other drying

methods. First, since drying takes place at low temperature, chemical decomposition is minimized. Second, the resulting product has a very high specific surface area, which promotes fast, complete dissolution of the dried product. This is a critical quality attribute for freeze-dried drugs used in emergency situations. Third, freeze drying is more compatible with sterile operations than dry powder filling, since the solution may be sterile filtered immediately before introduction into a vial and no powder handling steps are involved in the subsequent processing of a parenteral product particulate levels may be reduced to a minimum(9).

The cost of freeze drying is high because of equipment and energy but the cost of raw materials are low. Freeze drying is useful when the drug is unstable, heat labile and the product require minimum particulate matters, accurate dosing, requiring quick and complete rehydration and the high value product.

The principle of freeze drying may be divided into three stages; freezing, primary drying and secondary drying. Freezing is a critical step in the process, since the microstructure of both ice and solute formed during freezing that determines both the quality of the final product and its subsequent processing characteristics such as the rates of primary and secondary drying. The physical events of freeze drying are freezing process (super cooling), ice (primary) crystallization, concentration of the solutes during ice crystal growth, and crystallization of the solute(secondary) crystallization (9).

The freezing of the aqueous solution may first result in ice crystals form first at a temperature usually below $0^{\circ}C$. As the ice crystals form and grow throughout the system, the remaining solution (interstitial fluid) becomes more concentrated with the solute. If a solute forms a true eutectic with water, a eutectic phase consisting of finely divided crystals of the solute and ice crystallizes out and the whole system becomes solidified. The highest temperature at which this occurs has been termed the maximum temperature of complete solidification, T_{cs}. This is the temperature at which no liquid states exist in the product, and stability must be achieved if a solution is to be exposed for further freeze-drying process(9).

In the simple two-component systems, water and a solute may both crystallize. The freezing processes are cooling from the initial temperature to below $0^{\circ}C$ eventually results in the nucleation of ice. The releases of heat of crystallization raises the temperature toward $0^{\circ}C$ crystallization then proceed at a progressively falling temperature related to the equilibrium melting point of the concentration solution. As the temperature falls the solution becomes closer

to saturation so that crystals of solute are precipitated. Eventually a eutectic point is reached where the materials contain more than one crystallizable solute, a similar situation exists but the eutectic is lower than that of any two components combined. The eutectic temperature represents the maximum allowable product temperature during primary drying. While ice is still present and the product temperature exceeds the eutectic temperature, drying takes place from the liquid state instead of the solid state, and the desirable properties of the freeze-dried product are lost(9).

Primary drying is characterized by a boundary layer of ice in the vial. The driving force for sublimation of ice during primary drying is the difference between the vapor pressure of ice at the sublimation front and the partial pressure of water vapor in the freeze-dried chamber. Freeze drying can take place only under high vacuum if the driving force is determined only by differences in vapor pressure of water within the system. Freeze drying at atmospheric pressure must take place by molecular diffusion of water against a pressure gradient. Freeze drying process becomes more practical because of the freeze-dried chamber that can be rapidly pumped down to a total pressure less than the vapor pressure of ice in the product. During the primary drying state, one must take considerable measures to avoid two problems, eutectic melting and collapse (9).

Secondary drying involves the removal of absorbed water from the product. The water did not separate out as ice during the freezing and did not sublimate off. The residual moisture content determines the length of time devoted to secondary drying. In pharmaceuticals, the moisture contents of 1 % or less are the most desirable. Some desorption of water may occurs for the sublimation of ice in the secondary stage because of increasing in product temperature and decreasing in chamber pressure. However, the increase in product temperature may also cause product decomposition (9).

The interesting point of freeze-dried product is the effect of the processing conditions such as, freezing and heating rates in the freeze drying cycle to the final stability of the product (chemical and physical stability). The interesting effect of freeze drying cycle conditions on product stability is the potential to isolate the solid drug in a variety of physical states such as amorphous or different crystalline polymorphs. It is possible that each of polymorph can be expected to exhibit different chemical reactivity in the solid state and may have differing affinities for residual solvents with obvious stability implications of adequate characterization. If there is no adequate characterization of the various physical states in which the active drug can exist, the relative stability profiles, appropriate cycle design and control to insure consistent isolation of the

desired solid phase, the manufacturers should run the risk of producing a variable dosage forms which have very different physicochemical properties.

On the previous study, pralidoxime chloride has been used to develop and program product cycle of freeze drying by Patrick P. Deluca (11). In this study, pralidoxime chloride has a eutectic temperature of -10.8^{o}C and exhibits a considerable degree of supercooling. The complete solidification of pralidoxime chloride on freezing was not effected until a temperature below -30^{o}C and the initial drying temperature should not be higher than 16^{o}C. There is no study concerning polymorphism or solid state morphology of pralidoxime chloride (11).

Chongprasert et al studied the physical chemistry of freeze drying of the system glycine/water, with the emphasis on the role of polymorphism of glycine on freezing and freeze drying behavior (12). The researcher suggested, from personal contact, that pralidoxime chloride may have the different polymorph and the experiment should be set as the same as the study of glycine polymorphism. This study aim to observe and isolate the different form of pralidoxime chloride that may occurred during freeze drying process when different conditions were employed. Previous studies by other researcher showed no attempt was made to identify whether the different forms resulted solely from the freezing method or from the other process variables. The different polymorphs of drugs are known to display different physicochemical properties, chemical reactivity and stability. Polymorphism in solid is a well-known phenomenon that may impact both manufacturing and performance of a dosage form.

Objectives of the study

1. To investigate the existence of subambient eutectic formation of pralidoxime chloride solution by DSC.
2. To identify the freeze drying cycle of pralidoxime chloride solution.
3. To characterize the freeze dried product of pralidoxime chloride.