The Effect of Bulking Agent on the Solid-State Stability of Freeze-Dried Methylprednisolone Sodium Succinate

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The rate of hydrolysis of methylprednisolone sodium succinate in the freeze dried solid state at 40°C was determined in the presence of two common bulking agents - mannitol and lactose - at two different ratios of drug to excipient. Residual moisture levels were less than 1% in all samples tested, with no significant difference in residual moisture among different formulations. Rate of hydrolysis was significantly higher in mannitol-containing formulations versus lactose-containing formulations, and the rate of hydrolysis increases with increasing ratio of mannitol to drug. Thermal analysis and x-ray diffraction data are consistent with a composition-dependent rate of crystallization of mannitol in the formulation and its subsequent effect on distribution of water in the freeze-dried matrix. Increased water in the microenvironment of the drug decreases the glass transition temperature of the amorphous phase, resulting in an increased rate of reaction. The physical state of lactose remained constant throughout the duration of the study, and the rate of hydrolysis was not significantly different from the control formulation containing no excipient. Thermal analysis and x-ray diffraction data are consistent with formation of a liquid crystal phase in freeze-concentrated solutions of methylprednisolone sodium succinate containing no excipient.

KEY WORDS: thermal analysis; x-ray diffraction; excipients; crystallization; lyophilization.

INTRODUCTION

Bulking agents are commonly used in formulation of freeze dried products in order to provide an inert, easily reconstituted matrix containing a low dose of active drug substance. The study reported here was prompted by the need to prepare material for a blinded clinical trial where three different doses of drug are presented such that the freeze dried cakes all look alike by using an appropriate amount of a suitable bulking agent.

Methylprednisolone sodium succinate is a soluble prodrug of methylprednisolone used as an injectable corticosteroid, where solubilization is achieved through the use of the ionizable hemisuccinate moiety. The prodrug is unstable in aqueous solution, the principal products being hydrolysis to methylprednisolone and acyl migration to form the isomeric 17-ester (1). Therefore, methylprednisolone sodium succinate is marketed as a freeze dried powder (Solu-Medrol®).

The purpose of this study is to examine the effects of two of the most commonly used bulking agents in freeze dried injectable formulations - mannitol and lactose - on the stability of methylprednisolone sodium succinate as a freeze dried solid, with particular attention to the effect of excipient on the physical form of the freeze dried solid and the location of water within the solid matrix.

MATERIALS AND METHODS

Materials

Methylprednisolone hemisuccinate USP was provided by The Upjohn Company, Kalamazoo, MI. Mannitol and lactose were USP grade and were either provided by The Upjohn Company or purchased from Sigma Chemical Co. Phosphate buffer salts (Fisher Scientific) were analytical grade. Inorganic salts for water vapor adsorption experiments were reagent grade materials.

Methods

Drug with no excipient present (250 mg per vial) was used as a control for stability studies. Two strengths of drug were examined with each bulking agent - 40 mg and 125 mg - where the total amount of bulking agent plus drug was the same as the control. The formulation was prepared by suspending methylprednisolone 21-hemisuccinate in 0.08 M phosphate buffer, pH 7.5, containing the appropriate quantity of either mannitol or lactose. Conversion to the sodium salt was carried out by slow addition of 10% sodium hydroxide until essentially all solids were dissolved. The final pH was 7.5 - 7.7. Solutions were sterile filtered and 3.74 ml was filled into 20 ml tubing glass vials. Freeze drying was carried out by placing vials directly on the freeze dryer shelf, freezing at -50°C for 4-6 hrs, followed by primary drying at a shelf temperature of 10°C and a chamber pressure of 100 microns Hg for 24 hrs. Secondary drying was carried out for approximately 24 hrs at a shelf temperature of 30°C and a chamber pressure of 100 microns Hg. Vials were stopped under full vacuum. Residual moisture was measured by Karl Fisher titration (Model 701, Metrohm, Inc., Herisau, Switzerland) where the freeze dried material was quickly transferred to the titration vessel containing anhydrous methanol. Coulometric end point detection was used.

Stability of the freeze dried solid was measured at 25°C and 40°C using a reverse phase HPLC assay (1). A 4 μm Nova-Pak® C-18 column (Waters, Inc., Milford, MA) was used. The mobile phase consisted of 33% acetonitrile in water buffered at pH 5.2 - 5.4 with 0.05M acetate buffer. A fixed wavelength UV detector at 254 nm and digital data station were used to quantitate the parent compound and degrada-

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tion products. USP reference standards of methylprednisolone hemisuccinate and methylprednisolone were used as external standards. Percent methylprednisolone, the ester hydrolysis product, was used as the primary measure of chemical stability in the solid state.

Both the freeze dried solids and solutions prior to freeze drying were examined by thermal analysis using a Perkin-Elmer Series 7 DSC with a mechanical cooling accessory and computer data station (2). Helium (40 mL/min) was used as the purge gas. Solution samples were prepared by placing approximately 20 μL of solution in an aluminum sample pan and sealing the sample by crimping an aluminum cover in place. Samples were frozen at a controlled rate to about -50°C, and the thermograms were recorded during warming at a controlled rate to just above 0°C. A nitrogen-purged glove box was placed over the sample compartment to prevent artifacts due to moisture condensation. Solid samples were prepared by packing about 10 mg of freeze dried powder into aluminum sample pans. For measuring the effect of water vapor sorption on glass transition temperatures in the solid state, DSC pans containing the solid sample were placed in dessicators at different relative humidities and equilibrated for about 48 hours, at which time the samples were quickly removed from the dessicator and sealed. Thermograms were recorded in the range of 20-120°C.

Water vapor sorption isotherms were measured on freeze dried powders by placing vials (with lyostoppers in the partially inserted position) in dessicators containing various saturated salt solutions. The following salts were used - sodium hydroxide, lithium chloride, potassium acetate, potassium carbonate, and sodium bromide. Samples were removed at two hour intervals during the first 12 hours, followed by sampling twice a day for five days. Vials were sealed upon removal from the dessicator, and moisture content was determined by Karl Fisher titration. The water content of the samples was found to reach approximate equilibrium after about 48 hours at room temperature.

The physical form of the freeze dried powders was studied by x-ray powder diffraction. A Siemens Krystalloflex® diffractometer was used, with CuKα radiation at a voltage of 40 kV and a current of 20 mA. Powder specimens were prepared by gently breaking up the freeze dried cakes and placing in an aluminum powder mount. Samples were scanned from 2° to 40° at 0.1° per second.

RESULTS AND DISCUSSION

Effect of Bulking Agent on Stability

The stability at 40°C of the control formulation is shown in Figure 1 along with that of formulations containing 40 and 125 mg of drug in mannitol and 40 mg of drug in lactose. Each data point represents the average of duplicate measurements from different vials. Rate of hydrolysis of the drug with mannitol as the bulking agent is markedly faster than when lactose is used, and the rate of hydrolysis increases as the ratio of mannitol to drug increases. The rate of hydrolysis of the 40 mg strength in lactose is not significantly different from that of the control.

Residual moisture content of all formulations were in the range of 0.3 to 0.9% percent, and there was no significant difference in residual moisture between the samples containing mannitol and those containing lactose. There was a small but significant increase in residual moisture of all formulations during six months storage at 40°C, probably caused by water vapor transfer from the rubber stopper to the freeze dried cake. The average increase was 0.29% with a range of 0.05 - 0.45% and there was no significant difference between the formulations studied with respect to increase in residual moisture level.

Thermal Analysis

DSC thermograms of the formulations prior to freeze drying are shown in Figures 2-4. Note that endotherms are represented by upward deflections on all thermograms. Thermograms of methylprednisolone sodium succinate in phosphate buffer with no bulking agent present (Figure 2) are shown for three different heating rates after cooling at a rate of 20°C/min. Three separate thermal events occur prior to the melting endotherm of ice, and the thermograms recorded at different heating rates illustrate the effect of heating rate on both sensitivity and resolution. The endotherm on the leading edge of the ice melting endotherm is resolved at the slowest heating rate, but is not resolved at the highest heating rate. Two exotherms are observed prior to the endotherms, with best sensitivity in detecting the exotherms observed at higher heating rates.

The thermogram in Figure 2 is not consistent with low-temperature thermal behavior of solutions in which the solute a) crystallizes readily upon freezing, b) remains amorphous upon freezing, or c) initially forms a metastable amor-