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Research Article

Efficiency of Nanoliposomal Fluconazole Particle Produced by Spray Freeze Drying

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Abstract

Candidiasis is an important health problem, which is a common fungal infections with high mortality rate up to 70% especially in patients with immunosuppressive disorders. Pulmonary administration of drugs is mostly performed by wet nebulization. However, this form of pulmonary administration is time-consuming, carries the risk of patient reinfection and resistance building in the device, and is generally less patient friendly than a dry powder inhaler (DPI). Spray freeze drying (SFD) is a particle engineering technique that can be used to produce inhalable powder formulation. It is investigated in the food and pharmaceutical industries. Different formulations of fluconazole are prepared based on the amount of excipients desired. To determine the efficacy of the formulations and to evaluate the drug delivery pattern, one cc of each formulation is transferred to a dialysis bag and 100 cc of phosphate buffer is suspended in humans. Concentrations of 1000, 700, 500, 300, 300, 100, 10 g / ml were made from fluconazole in water and 80 tween and their absorption at 261 nm was determined by UV spectrophotometer. They are present through nanoparticles, but by increasing the ratio of fluconazole in these formulations by a ratio of 1:1, the rate of release of these drugs is reduced. In this study, sugar expanses were used to make inhaled formulations of fluconazole. In general, these expanses have been used to improve dispersion, whether for the purpose of adding carrier or for the purpose of additive.

Keywords: Candidiasis, Nebulization, Spray Freeze Drying, Fluconazole

INTRODUCTION

Candidiasis is an important health problem, which is a common fungal infections with high mortality rate up to 70% especially in patients with immunosuppressive disorders. The disease is difficult to treat particularly during serious damage to the immune system, which could cause invasive candidiasis and deep-seated tissue infection. The separation of Candida species in the respiratory, digestive, and urogenital systems are not easy, because they could be a form of normal flora at the mucosal area. High doses of antifungal are needed to achieve fungicidal concentrations at the infected sites. However, only a small part of orally or intravenously used antifungal drug attains to lung or orophagial infected site. This leads to sub-dosage antifungal concentrations at the sites of infection, which develops the chance of fungal resistance, while high systemic dosage could cause toxic drug reactions. So more targeted drug delivery could have important improvements in the treatment of these infections.

One such targeted route of administration is the pulmonary route. Use of this route permits a higher fraction of the administered antifungal to reach the infected lungs(1-15). As a result, higher local concentrations are attained, which may even exterminate funguses that are considered resistant. With the lower systemic exposure resulting from a more targeted approach, systemic side effects (such as hepatotoxicity) are reduced.

Currently, pulmonary administration of drugs is mostly performed by wet nebulization. However, this form of pulmonary administration is time-consuming, carries the risk of patient reinfection and resistance building in the device, and is generally less patient friendly than a dry powder inhaler (DPI). In contrast, a dry powder formulation in combination with a DPI would not require all these prerequisites to function and, therefore, is more suitable for large-scale usage in these areas.

As described above, the best approach to increase the concentration of the drug in the lungs is pulmonary administration. To date, the challenge of formulating fluconazol in an appropriate dry powder for pulmonary administration has received scant attention in the research literature.

While many studies on inhaled antifungal formulations focus mainly on amphotericin B, there are limited studies that investigate the inhaled powder formulations of triazoles.

Spray freeze drying (SFD) is a particle engineering technique that can be used to produce inhalable powder formulation. It is investigated in the food and pharmaceutical industries.

This advanced particle engineering method involves a feed liquid being atomized into fine droplets, which are frozen instantaneously by cryogenic liquid, and subsequently the frozen solvents are sublimed at low temperature and pressure. Porous particles are formed due to the sublimation of ice crystals. Their aerodynamic qualities, because of the relatively low density, have made this technology an attractive method for producing powder aerosol for inhalation. Moreover, the porous structure of the SFD powders could enhance the apparent solubility of the formulation, which is important for pulmonary delivery.

Currently, freeze-drying is the most commonly used technique for dehydration of pharmaceutical products. Further, conventional lyophilization is a time-consuming process. Rapid cooling of aqueous solutions is reported to minimize the formation of ice nuclei and crystalline water, which might prevent disruption of the liposomal structure and denaturation of proteins and peptides. The spray freeze-drying (SFD) technique may be superior for producing protein-loaded liposomal products, and is growing in popularity for the formulation of solid pharmaceuticals. In the SFD process, an aqueous formulation containing bioactives is sprayed directly into a cryogenic medium such as liquid nitrogen, rapidly freezing the atomized droplets and forming microparticles. The frozen particles are collected and lyophilized, leaving behind dry particles. Because the entire SFD process is conducted under subambient conditions, it is particularly suited for drying heat-labile materials. However, few reports about the use of SFD with nanoparticles or liposomes have been published. The influence of the SFD process on the character of liposomes and its encapsulation efficiency remains unknown.

This study designed to formulate nanoliposomal fluconazole particle by SFD and evaluate the efficiency of the product.

MATERIALS AND METHOD

Different formulations of fluconazole are prepared based on the amount of excipients desired. First, we dissolve 50 mg of fluconazole in 5 cc of acetone and then add the desired amount of excipients to the solution according to Table 1-2 and put it in a balloon. Place the beaker at 30 ° C to dissolve the expanse in the acetone solution. Slowly add 5 cc of acetone solution to 5 cc of 2% polyvinyl alcohol solution containing the probe of the sonicator in one minute and one minute after adding the solution to the 2% polyvinyl alcohol solution. Leave to form an emulsion containing SLN or PLN. Then transfer the final solution to a 100 cc bottom balloon and use a rotary evaporator at a speed of 25 RPM at low pressure under a vacuum pump and take 10 to 15 minutes to remove the organic solvent which is acetone from the solution. To prepare the dry powder for inhaled PLNs and SLNs, we first pelleted the colloids made of nanoparticles with a centrifuge at 14,000 rpm to separate the nanoparticles from the PVA solution. After washing 3 times dissolve certain amounts of lactose or in 5 ml of distilled water and add to the nanoparticles. Immediately after preparing the nanoparticle solution, you sprayed it with a peristaltic pump at a speed of 5 ml per minute and using a nozzle at 250 cc of energy. The frozen particles were then transferred to a -80 ° C refrigerator. The resulting particles were dried with a freezer at -55 ° C for 48 hours and the resulting powder was collected and stored in a completely dry vial. Formulated SLN formulations contain varying amounts of these nanoparticles. To determine the efficacy of the formulations and to evaluate the drug delivery pattern, one cc of each formulation is transferred to a dialysis bag and 100 cc of phosphate buffer is suspended in humans. Due to the low solubility of fluconazole in A and in order to create sink conditions, 100 mg of tween 80 was added to the phosphate buffer. Then, at different times, 2 cc of phosphate buffer in human was sampled each time and the uptake of the samples was obtained using UV spectrophotometry and the concentration of the samples was calculated at different times. Then, from the obtained information, time-rate release diagrams of the formulations were drawn.

RESULTS

Concentrations of 1000, 700, 500, 300, 300, 100, 10 g/ml were made from fluconazole in water and 80 tween and their absorption at 261 nm was determined by UV spectrophotometer.

According to the standard curve diagram, the relationship between adsorption and concentration can be evaluated in the range of 10-10 g/mlμ and the data related to the variables had a good correlation with $R^2 = 0.992$. To investigate how the formulations were released, samples were taken at

different times and the adsorption of the samples was read by UV spectrophotometry and the soluble concentrations were calculated at different times.

For each of the formulations, using the concentration of the solution at different times, the percentage of drug release at different times was calculated and based on that, time-percentage release diagrams were drawn. As can be seen, nanoparticles containing polycaprolactone have the slowest drug release. However, the use of PLGA in nanoparticle formulations also effectively helps to release the drug slowly. In this ability, nanoparticles containing fatty substances (SLN) have less effect in inhibiting drug release

They are present through nanoparticles, but by increasing the ratio of fluconazole in these formulations by a ratio of 1: 1, the rate of release of these drugs is reduced.

DISCUSSION

In this study, spray freeze drying method was used to produce SLN and PLN particles, which was first prepared by solutions containing different amounts of lipid particles such as SLN and PLN containing polymeric materials such as PLGA and PCL, and then by freeze-spray spray dry powder method.

Inhalation income: This method has limitations such as low product volume, which is suitable for laboratory work but not for industrial scale. In the process of making and preparing the formulation, the container and materials must be completely clean. In fact, in the process of making SLN suspension in spray freezing method, the sequence of preservation steps and aqueous and organic phases should not be mixed together. Vacuum intensity and duration under vacuum in the solvent removal phase are important depending on the solvent removal conditions (tank temperature), the organic phase used and the vacuum pump power. In the experiments related to this study, the solvent averaged between 10 It was vacuumed for 15 minutes until the acetone was completely drained from the tank. There are various methods for producing dry inhaled powder, which in this study used freeze-spray spray method. Freeze-spray method is a method in which particles with high porosity and geometric diameter and aerodynamics suitable for drug delivery are produced by inhalation.

In this study, sugar expanses were used to make inhaled formulations of fluconazole. In general, these expanses have been used to improve dispersion, whether for the purpose of adding carrier or for the purpose of additive.

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