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Particle design of itraconazole by evaporative recrystallization for dissolution improvement

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ABSTRACT

The aim of this study was to improve dissolution of a poorly water-soluble drug, itraconazole (ITZ), by evaporative recrystallization under vacuum using lyophilizer and rotary evaporator, and compared with that prepared under the ambient conditions. Different organic solvents were used as crystallizing solvent. The amorphous ITZ was obtained by vacuum evaporation using lyophilizer and rotary evaporator. Immediate evaporation of chloroform or methylene chloride out from the drug solution caused the rapid crystallization, leading to amorphous phase formation. Using chloroform as crystallizing solvent caused the complete amorphous ITZ while some ITZ crystals were still found when using methylene chloride. Thus, the dissolution of amorphous ITZ obtained from chloroform showed better dissolution than that from methylene chloride. The crystallization method also influenced the properties of ITZ powders. The ITZ powders prepared from vacuum evaporation using both rotary evaporator and lyophilizer showed a significant increase in drug dissolution. By using lyophilizer, the ITZ powders with faster dissolution were obtained. This is because extremely low temperatures can limit molecular mobility, therefore, the nucleation of the drug is prevented, and crystallization cannot occur, leading to complete amorphous phase formation. After 1-year storage at ambient conditions, both ITZ powders were partially crystallized, leading to a decrease in dissolution. However, ITZ powders obtained from vacuum crystallization using lyophilization showed less change and still provided higher drug dissolution. The instability of the amorphous ITZ was expected and confirmed by these experiments. Therefore, stabilization of the amorphous ITZ is necessary to maintain the drug effectiveness through a long-term storage.

1. Introduction

Evaporative recrystallization is one of the simple crystallization methods. The supersaturation of the drug solution can be achieved by removal of some of solvent (Mullin, 1995). The evaporation can be performed by various methods, e.g., fusion-cooling, spray-drying, rotary evaporation, lyophilization and evaporation in ambient conditions (Priyanka et al., 2008; Tian et al., 2009; Elgindy et al., 2010). Vacuum evaporation can reduce pressure in a liquid-filled container to be below the vapor pressure of the liquid, causing the liquid to evaporate at a lower temperature than normal. The crystallization occurs

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rapidly, leading to amorphous solid formation which gave better solubility and dissolution than its crystal form (Gupta and Sehrawat, 2011).

The enhancements of dissolution and in vivo absorption by pharmaceutical amorphous solid are reviewed in numerous articles (e.g., Sarkari et al., 2002; Papageorgiou et al., 2006; Overhoff et al., 2007). Amorphous drugs are formed either by prevention of crystal lattice formation (rapid solidified or phase separation) or by disruption of an existing crystal structure (possessing energy or desolvation) (Jozwiakowski, 2000). For example, cooling of the melt can produce the amorphous form of drugs. When a crystalline solid is heated beyond its melting temperature and cooled back, the liquid will become amorphous at temperatures below its melting point if sufficient time is not allowed for nucleation to occur. As reported by Six et al. (2001a,b), the glassy itraconazole was formed by cooling from the melt. In contrast to their advantage in dissolution enhancement, amorphous solids have low stability. The amorphous solids, which are not thermodynamically stable, can recrystallize into crystalline form during the storage (Jozwiakowski, 2000). Therefore, a stabilization system is necessary to maintain the amorphous drug through shelf-life.

The rotary evaporation is normally used for evaporating the solvents from a mixture. A rotary evaporator consists of a heated rotating vessel, which is maintained under a vacuum through a tube connecting it to a condenser. The temperature of rotating flask is controlled by partial emersion and rotating in a water bath which provides a good heat transfer and prevents the bumping caused by superheating of the liquid. The solvent vapors leave the flask by the connecting tube and are condensed in the condenser part. The major advantages of this method are the ability to rapidly remove large quantities of solvent and recover the solvent. The report about using of rotary evaporator for recrystallization is still limited, but it is generally suggested in solid dispersion preparations in order to prepare amorphous drug incorporated in carriers (Biswal et al., 2009).

Lyophilization, so called freeze-drying, is carried out using sublimation process to remove solvent out of samples. Sublimation is the transition of a substance from the solid to the vapor state, without first passing through an intermediate liquid phase. Lyophilization is often used to prepared amorphous materials. In this case, extremely low temperatures are used to limit molecular mobility, and to prevent nucleation of the drug and the excipients, therefore, the condition of lyophilization can have a major influence on solid phase of the drug (Zhou et al., 2009). It is reported that using of lyophilization in preparation of the solid dispersion provided higher drug dissolution than using of rotary evaporation (Betagari and Makarla, 1995).

Typically, a slow evaporative crystallization of pure drug will not provide the amorphous substance due to the sufficient time for drug molecules to arrange orderly as crystalline solid. However, the polymorphic form of drugs can be changed after the crystallization using some additives (Tian et al., 2009). In this study, the evaporative recrystallization using rotary evaporation and lyophilization methods were demonstrated and used for preparing amorphous form of ITZ, without carrier, in order to improve dissolution of the drug. The evaporative crystallization under the ambient conditions was also performed, in order to compare the crystal properties with the prepared amorphous drugs.

2. Materials and methods

2.1. Materials

ITZ raw material used in this study was purchased from Nosch Labs Private (India). Chloroform (Merck, Germany) and methylene chloride (QReC, New Zealand) were used as crystallizing solvent in halide group while methanol (Merck, Germany), ethanol (Liquor Distillery Organization, Thailand), and isopropanol (Merck, Germany) were used as crystallizing solvent in alcohol group. Polyethylene glycol (PEG) 200 and PEG 400 were from Fluka (Germany). Distilled water was used as an anti-solvent in recrystallization of ITZ from alcohols and PEGs while hexane (Labscan, Thailand) was used as an anti-solvent for water-immiscible solvents. Other chemicals were of reagent or analytical grade and used without further purification. The simulated gastric fluid USP without pepsin (SGF) was prepared by dissolving 2 g of sodium chloride and 7 mL of hydrochloric acid into distilled water and adjusting volume to 1000 mL, pH to 1.2, and used as dissolution medium.

2.2. Evaporative recrystallization

A proper amount of ITZ was dissolved in different solvents, e.g., chloroform, methylene chloride, methanol, ethanol, isopropanol, to get a saturated ITZ solution. The volatile solvent was then evaporated under three conditions, i.e., ambient conditions, rotary evaporation and lyophilization. In the ambient conditions, solvent was evaporated by continuous stirring for 12 h in a fume hood, at 25 °C. By vacuum evaporation using rotary evaporator, a rotary evaporator (Rotavapor R-3, Buchi, Switzerland) was used to provide a low pressure condition of 100 mbar, at 25 °C. ITZ solution was inside the evaporation flask until white crystals of ITZ appeared. The drug crystals were continuous rotated for 2 h to ensure that there is no solvent left. In the vacuum evaporation using lyophilizer, ITZ solution was pre-frozen in liquid nitrogen and then placed in a lyophilizer (Freezone 2.5, Labconco, USA) for 24 h in which solvent was evaporated under 0.29 mbar and −49 °C. The drug crystals were collected after drying and kept in a desiccator.

2.3. Morphology examination

The morphology of ITZ crystals were investigated using a scanning electron microscope (SEM; S-2500, Hitashi, Japan) under an accelerating voltage of 15 keV. Crystal samples were fixed on SEM stubs with double-sided adhesive tape and then coated in a vacuum with thin gold layer before investigation.

2.4. Hot-stage microscopy

The thermal properties of ITZ after treatment by various conditions were investigated by hot-stage microscopy. The samples were heated by a hot-stage (FP82HT, Mettler Toledo, Switzerland) at the scanning speed of 1 °C/min and observed under an optical microscope (CX41, Olympus, Japan). Changes in the morphology (melting or crystallization) were noted as a function of temperature. The polarization properties of ITZ were also observed during the experiment using a polarized filter (CX-AL, Olympus, Japan) to investigate the crystal properties.