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Continuous production of itraconazole-based solid dispersions by hot melt extrusion: Preformulation, optimization and design space determination

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ABSTRACT

The purpose of this work was to increase the solubility and the dissolution rate of itraconazole, which was chosen as the model drug, by obtaining an amorphous solid dispersion by hot melt extrusion. Therefore, an initial preformulation study was conducted using differential scanning calorimetry, thermogravimetric analysis and Hansen's solubility parameters in order to find polymers which would have the ability to form amorphous solid dispersions with itraconazole. Afterwards, the four polymers namely Kollidon® VA64, Kollidon® 12PF, Affinisol® HPMC and Soluplus®, that met the set criteria were used in hot melt extrusion along with 25 wt.% of itraconazole. Differential scanning confirmed that all four polymers were able to amorphize itraconazole. A stability study was then conducted in order to see which polymer would keep itraconazole amorphous as long as possible. Soluplus® was chosen and, the formulation was fine-tuned by adding some excipients (AcDiSol®, sodium bicarbonate and poloxamer) during the hot melt extrusion process in order to increase the release rate of itraconazole. In parallel, the range limits of the hot melt extrusion process parameters were determined. A design of experiment was performed within the previously defined ranges in order to optimize simultaneously the formulation and the process parameters. The optimal formulation was the one containing 2.5 wt.% of AcDiSol® produced at 155 °C and 100 rpm. When tested with a biphasic dissolution test, more than 80% of itraconazole was released in the organic phase after 8 h. Moreover, this formulation showed the desired thermoformability value. From these results, the design space around the optimum was determined. It corresponds to the limits within which the process would give the optimized product. It was observed that a temperature between 155 and 170 °C allowed a high flexibility on the screw speed, from about 75 to 130 rpm.

1. Introduction

In the last years, pharmaceutical industry has been using advanced techniques such as high throughput screening and computational chemistry in order to discover new molecules as potential active pharmaceutical ingredients (API) (Alsenz and Kansy, 2007; Lipinski et al., 2001). However, the identified potential drug candidates show complex chemical structures which results in 70% of drug candidates having poor water solubility (Ku and Dulin, 2012; Loftsson and Brewster, 2010). Among this 70%, 40% are even considered as practically insoluble

Abbreviations: API, active pharmaceutical ingredient; BCS, biopharmaceutics classification system; DoE, design of experiments; DS, design space; DSC, differential scanning calorimetry; FDA, food and drug administration; HME, hot melt extrusion; HPLC, high performance liquid chromatography; ITZ, itraconazole; nd, non-detected; T_{deg}, degradation temperature; T_g, glass transition temperature; TGA, thermogravimetric analysis; T_m, melting temperature; USP, United States Pharmacopoeia.

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(<100 μg/mL) (Takagi et al., 2006). These compounds mostly belong to the second class of the biopharmaceutics classification system (BCS) described by Amidon et al. in 1995. One useful method for increasing the solubility of these APIs is to convert the crystalline form into its amorphous form to obtain amorphous solid dispersions (Bellantone, 2014; Kawabata et al., 2011). In order to increase the stability of the amorphous component, a one-phase miscible drug-polymer system must be formed. Otherwise, due to the lack of structure, the unstable amorphous form will recrystallize.

The two most common techniques used to generate amorphous solid dispersions in the pharmaceutical field are hot melt extrusion (HME) and spray drying. Some techniques using supercritical fluids such as supercritical fluid impregnation have also been described recently (Potter et al., 2015). HME presents many advantages, such as the possibility of working without solvents, which is not the case for spray drying, thus avoiding the need for subsequent drying steps (Bruce et al., 2005). Furthermore, it is a low cost process that allows fast production with a small ecological footprint and the ability to work continuously (Thiry et al., 2015).

In order to form stable amorphous solid dispersions, the drug and the polymer must be in a liquid state, through melting or dissolution then properly mixed and finally solidified. Another important aspect to consider is the affinity between the API and the polymer, especially when aiming for enhancement of the bioavailability of poorly soluble drugs (Shah et al., 2013). Indeed, the interactions between the polymer and the API will prevent the API from recrystallizing. It is for this reason that a screening process of different polymers is generally required in order to find the most adequate polymer (Baghel et al., 2016; Sarode et al., 2012).

The release of the API and the quality of the final product can be tuned by adding some excipients to the main polymer. Indeed, disintegrants, solubilizers, crystallization inhibitors or fillers can be added to the formulation in order to increase the dissolution rate of the API. These excipients can be added after the milling of the extrudates before being compressed into a tablet (Agrawal et al., 2016; Lang et al., 2016) or during the HME process (Rambali et al., 2003). The formulation step is therefore critical because it will have a major impact on the final product quality.

However, since extrusion is a complex process which is very versatile and flexible, the process parameters should also be taken into account in order to obtain the best final product (Romanski et al., 2013). Indeed, the limits of the process, between which the final product meet the previously set expectations, must be determined; this is called the “design space” (DS). Nowadays, the food and drug administration (FDA), other regulatory agencies and standard-setting organizations are willing to establish quality by design guidance relevant to the requirements of the pharmaceutical industry (U.S. Department of Health and Human Services Food and Drug Administration, 2004). They suggest the use of design of experiments (DoE) so that it would provide a structured and organized method for determining the relationship between factors affecting a process and the response of that process to the changing of these factors (Thiry et al., 2015).

In this study, itraconazole (ITZ) was chosen as the model BCS II molecule. The purpose of this work was to increase the solubility of ITZ as well as its dissolution rate by obtaining an amorphous solid dispersion by a HME process. Therefore, an initial preformulation study was conducted in order to select polymers which would be able to form amorphous solid dispersions with ITZ and keep ITZ amorphous as long as possible. When a suitable polymer was selected, the formulation was fine-tuned by adding some excipients during the HME process in order to increase the release rate of ITZ. In parallel, the range limits of the HME process were determined. Afterwards, a DoE was performed within the previously defined ranges in order to optimize simultaneously the formulation and the process parameters. From these results, a DS was finally determined in order to set the limits within which the process would give the optimized product.

2. Experimental section

2.1. Materials

ITZ was supplied by Exim Corporation (Mumbai, India). Kolliphor® P188, Kollidon® VA64, Kollidon® 12PF, Kollidon® CL and Soluplus® were kindly donated by BASF (Ludwigshaven, Germany). Eudragit® polymers were donated by Evonik (Darmstadt, Germany); Affinisol® HPMC, Methocel® and Ethocel® by Dow Chemicals (Staines, UK) and HPMCP and Aquoat® AS by Shin-Etsu (Tokyo, Japan). Sporanox® (Janssen, Belgium) was purchased at a local pharmacy. Lactose 100 Mesh was purchased from DFE Pharma (Gosh, Germany). Croscarmellose Sodium (AcDiSol®) was purchased from FMC Biopolymer (Philadelphia, USA) and sodium bicarbonate (Ph. Eur.) was supplied by Merck (Darmstadt, Germany). Sodium starch glycolate (Glycolys®) was kindly donated by Roquette (Lestrem, France). Acetonitrile (HPLC grade) was purchased from J.T. Baker (Deventer, The Netherlands), octanol (general purpose grade), chloroform (general purpose) from Fisher Scientific (Loughborough, UK), sodium hydroxide from VWR International (Radnor, USA), hydrochloric acid (37% (wt.%) for analysis) and monosodium phosphate (Ph. Eur.) from Merck (Darmstadt, Germany). Water was purified *via* a Millipore® system (18.2 MΩ/cm resistivity, Milli-Q) before filtration through a 0.22 μm Millipore Millipak®-40 disposable filter units (Millipore Corporation, USA).

2.2. Preformulation study

2.2.1. Thermogravimetric analysis

Thermogravimetric analysis (TGA) was used to determine the degradation temperature of the polymers. Approximately 10 mg of polymer was placed in a small pan in platinum. The pan was then hung on a high precision balance before being introduced in a hermetic furnace. The sample is then heated. The machine records the weight loss of the sample as a function of temperature. The device used was a TGA Q 500 (TA Instrument, New Castle, USA). The samples were heated from room temperature to 600 °C at a rate of 50 °C/min.

2.2.2. Differential scanning calorimetry

Differential scanning calorimetry (DSC) was used to determine the glass transition temperatures (T_g) of the polymers. 8–12 mg of powder were weighted accurately, crimpled in an aluminum pan than subjected to two heating–cooling cycles. The heating and cooling rates were both 10 °C/min ranging from 25 °C to maximum 200 °C depending on the TGA results. Indeed, when measuring the T_g, the maximum working temperature should always stay below the degradation temperature (T_{deg}). The equipment used for this study was a Mettler-Toledo® DSC 1 (Schwerzenbach, Swiss) controlled by the STARe System software.

2.2.3. Film casting

Physical mixture with varying rations of polymer and ITZ were dissolved in a minimum of chloroform (30/70 wt.%, 50/50 wt.% and 70/30 wt.%). The solution was then casted on a glass plate to obtain a thin film. If the film was translucent, the solid solution was considered amorphous and if the film was opaque or spotted, it was considered crystalline.