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Investigation of a suitable *in vitro* dissolution test for itraconazole-based solid dispersions

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ABSTRACT

The difficulty to find a relevant *in vitro* dissolution test to evaluate poorly soluble drugs is a well-known issue. One way to enhance their aqueous solubility is to formulate them as amorphous solid dispersions. In this study, three formulations containing itraconazole (ITZ), a model drug, were tested in seven different conditions (different USP apparatuses and different media). Two of the formulations were amorphous solid dispersions namely Sporanox®, the marketed product, and extrudates composed of Soluplus® and ITZ produced by hot melt extrusion; and the last one was pure crystalline ITZ capsules. After each test, a ranking of the formulations was established. Surprisingly, the two amorphous solid dispersions exhibited very different behavior depending primarily on the dissolution media. Indeed, the extrudates showed a better release profile than Sporanox® in non-sink and in biphasic conditions, whilst Sporanox® showed a higher release profile than the extrudates in sink and fasted simulated gastric conditions. The disintegration, dynamic light scattering and nuclear magnetic resonance results highlighted the presence of interaction between the surfactants and Soluplus®, which slowed down the erosion of the polymer matrix. Indeed, the negative charge of sodium dodecyl sulfate (SDS) and bile salts interacted with the surface of the extrudates that formed a barrier through which the water hardly diffused. Moreover, Soluplus® and SDS formed mixed micelles in solution in which ITZ interacts with SDS, but no longer with Soluplus®. Regarding the biphasic dissolution test, the interactions between the octanol dissolved in the aqueous media disrupted the polymer — ITZ system leading to a reduced release of ITZ from Sporanox®, whilst it had no influence on the extrudates. All together these results pointed out the difficulty of finding a suitable *in vitro* dissolution test due to interactions between the excipients that complicates the prediction of the behavior of these solid dispersions *in vivo*.

1. Introduction

One of the most critical issues in the pharmaceutical industry for many decades has been poorly soluble drugs. Recent estimates suggest that approximately 70% of drugs within pharmaceutical pipelines possess a low aqueous solubility. Moreover, almost 40% of marketed oral drug products are considered poorly soluble, with an aqueous solubility of less than 100 μg/mL (Loftsson and Brewster, 2010). Those compounds mostly belong to the second class of the Biopharmaceutics Classification System (BCS) described by Amidon et al. in (1995).

One possible solution to this problem is by converting the crystalline drug into its amorphous form. Since the amorphous form possesses a higher level of free energy than the crystalline one, the kinetics of dissolution increases due to the reduced energy barrier (activation energy). Moreover, the crystalline structure is broken and therefore the aqueous solubility of the compound drastically improves (Bellantone, 2014). However, due to the lack of structure and higher free energy, the amorphous form is inherently unstable and tends to recrystallize. In order to increase the stability of the amorphous component, a one-phase miscible drug-polymer system can be formed. The formation of a system exhibiting a negative Gibbs free energy of mixing thus stabilizes the amorphous form of the drug (Tian et al., 2013). To form a stable amorphous solid dispersion, 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

Abbreviations: API, Active pharmaceutical ingredient; BCS, Biopharmaceutics Classification System; CPMAS, Cross-Polarization Magic-Angle Spinning; DLS, Dynamic light scattering; DOSY, Diffusion Ordered SpectroscopY; DSC, Differential scanning calorimetry; DSS, 3-(Trimethylsilyl)-1-propanesulfonic acid sodium salt; FaSSGF, Fasted state simulated gastric fluid; FID, Free induction decays; HME, Hot melt extrusion; HPLC, High Performance Liquid Chromatography; ITZ, Itraconazole; NMR, Nuclear magnetic resonance; SDS, Sodium dodecyl sulfate; SOL, Soluplus®; TGA, Thermogravimetric analysis; USP, United States Pharmacopeia.

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the API and the polymer matrix, especially when aiming for enhancement of the bioavailability of poorly soluble drugs (Shah et al., 2013). It is for this reason that a screening process of different polymers is generally required in order to obtain the best solid dispersion (Sarode et al., 2012). The two most common techniques used to generate 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). The increasing popularity of HME is evident as pharmaceutical industries have introduced excipients for oral administration dedicated to HME, such as Dow Chemicals (e.g. Affinisol® HME) or BASF (e.g. Soluplus®). Soluplus® was specifically designed to enhance the solubility of a poorly soluble drug using the HME process (Hardung et al., 2010). It is an amphiphilic block copolymer composed of a polyethylene glycol 6000 backbone grafted with a random copolymer of polyvinylcaprolactam and polyvinylacetate as shown on Fig. 1A. This polymer, which was brought to the market in 2010, has been used extensively to improve the solubility of the BCS class II drugs (Hardung et al., 2010; Linn et al., 2012).

However, the evaluation of the solubility enhancement of the BCS class II drugs *in vitro* can be problematic since aqueous media fail to provide ideal conditions for these compounds. The dissolution method development can be a real challenge because of low drug release and slow release rates (Phillips et al., 2012a). Regarding the recommendations of the European Pharmacopeia (EP) (Convention, 2011) and the United States Pharmacopeia (USP) (Pharmacopoeia, 2010), the use of sink-conditions is highly recommended. The methods to reach sink-conditions with such low-solubility compounds are either via the use of larger volumes of aqueous dissolution media (Chiou and Riegelman, 1970; Katchen and Symchowicz, 1967; Symchowicz and Katchen, 1968) or through alternative dissolution systems such as the flow-through apparatus (USP Apparatus IV) in an open-loop configuration (Butler and Bateman, 1998; Posti and Speiser, 1980). Clearly, the biggest disadvantages of these techniques are the high consumption of dissolution media and the limitations regarding detection by analytical methods. A possible solution is by using a surfactant in order to reach sink conditions. The addition of surfactants, such as sodium dodecyl sulfate (SDS) or Tween®, to the dissolution media is one of the most documented methods and is especially useful for the dissolution of immediate-release products (Chen et al., 2003; Matteucci et al., 2009). Since surfactants are amphiphilic compounds used in large quantities in the dissolution media (up to 1%; %w/v) and may even be charged, they are prone to interact with the excipients present in the formulation. This observation has been reported in the case of cellulose ethers with SDS (Alli et al., 1991; Daly et al., 1984; Nilsson, 1995; Saito, 1960). This was also reported for SDS with methyl cellulose (Lewis and Robinson, 1970; Saito et al., 1971), polyvinylpyrrolidone (Misselyn-Bauduin et al., 2001), polyethylene glycol (Jones, 1967), polyvinyl acetate (Goddard, 1986) and for Tween® 20 and 80 with polyethylene glycols (Mahajan et al., 2004). Since these interactions can alter the mechanism of API release and therefore lead to an irrelevant release profile, the addition of surfactants in the dissolution media requires careful consideration.

Alternative dissolution media can also be used. In recent years, working with simulated gastric or intestinal fluids has emerged as a popular topic within the literature (Janssens et al., 2008; Kogermann et al., 2013; Sun Dong et al., 2000). Those media composed of surfactants, organic salts and lipid compounds are expected to mimic the gastric and intestinal environments under fasted or fed state conditions in order to provide a better *in vitro–in vivo* correlation (Dressman and Reppas, 2000). However, the presence of surfactants and salts might modify the drug release profile due to interactions with the excipients (Vogtherr et al., 2015).

Another possibility, which to date has not been explored as extensively, would be working under non sink-conditions. Dissolutions tests under non-sink conditions are currently less popular than others because this simplistic medium is unlikely to reflect what would happen *in vivo* (Alsarra et al., 2010; Miller et al., 2007).

Already in 1966, Levy mentioned the use of a biphasic dissolution test (Levy, 1966). He suggested that the presence of an upper organic phase within the dissolution medium could be used as a reservoir for the dissolved drug. Briefly, the model utilizes a dissolution medium consisting of immiscible aqueous and organic solvents. Dissolution of the drug in the aqueous layer is followed by a partitioning–transfer step which exploits the lipophilicity (log P) of the compound. After the transfer to the organic phase, the aqueous phase would be able to dissolve increased drug quantities and consequently the dissolution–partition cycle would continue. Due to this phenomenon, the biphasic dissolution test could be considered more biorelevant because the aqueous phase would mimic the stomach whilst the organic phase would mimic the absorption to the blood stream. Moreover, due to the transfer of the dissolved drug from the aqueous phase to the organic phase, the aqueous medium is not saturated. This unusual test has been reported in the literature for the testing of poorly soluble drugs (Chaudhary et al., 1994; Gibaldi and Feldman, 1967; Grundy et al., 1997a,b; Pestieau et al., 2015; Phillips et al., 2012a,b; Shi et al., 2010; Thu Hoa and Kinget, 1996).

The purpose of this study was initially designed to select a suitable *in vitro* dissolution test in order to evaluate the solubility enhancement of itraconazole (ITZ — Fig. 1B), as the model BCS class II drug, when formulated as solid dispersions. Two different solid dispersions will be compared, namely Sporanox®, which is the marketed oral capsule, and extrudates composed of Soluplus® produced by HME as well as the pure crystalline ITZ. In the literature, at least two *in vivo* studies evaluated the solubility enhancement of ITZ — Soluplus® solid dispersions and compared it to Sporanox®. These *in vivo* studies were conducted either on rats or dogs (Linn et al., 2012; Zhang et al., 2013) and

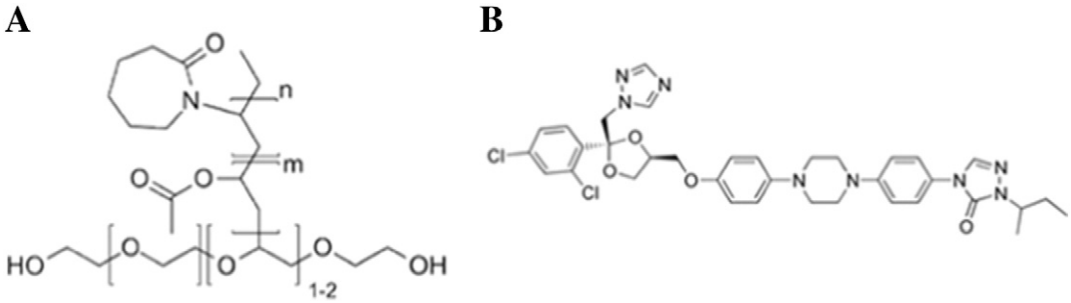

Fig. 1. Molecular structure of Soluplus® (A) and ITZ (B).