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Research Paper

Design of spray dried ternary solid dispersions comprising itraconazole, soluplus and HPMCP: Effect of constituent compositions

Mark T. Davis[a,*], Catherine B. Potter[a], Maryam Mohammadpour[b], Ahmad B. Albadarin[a], Gavin M. Walker[a]

[a] Synthesis and Solid State Pharmaceutical Centre (SSPC), The BernalInstitute, University of Limerick, Ireland
[b] School of Pharmacy, Cavanagh Pharmacy Building, NUI, Cork, Ireland

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ABSTRACT

A range of 17 ternary formulations of itraconazole (ITZ), HPMCP and Soluplus have been manufactured using spray drying. These amorphous solid dispersions (ASDs) were very stable against crystallisation and ITZ was found to be amorphous in all formulations after one year at 40 °C/75% RH. A number of solid state analytical techniques including PXRD, DSC, small angle X-ray scattering, FTIR and solid state NMR were used to characterise the physicochemical properties of the ASDs following processing and storage and to assess any interactions between components. Microtrac laser scattering analysis revealed a relationship between polymer levels and particle size distribution (PSD). Dissolution studies indicated that higher Soluplus content in the formulation resulted in higher concentrations of ITZ in acidic media.

1. Introduction

Despite the disparity between the significant research efforts in the past four decades and the number of successfully introduced systems into the market, the preparation of amorphous solid dispersions (ASDs) still holds a key position among the various formulation approaches intended to improve the dissolution rate of BCS II compounds (Guns et al., 2011). With higher Gibbs free energy than their crystalline counterparts, amorphous systems possess greater apparent aqueous solubility but are thermodynamically unstable, exhibiting a tendency towards spontaneous crystallisation. To enhance the physical stability of pure amorphous active pharmaceutical ingredient (API) a carrier, often an amorphous polymer, can be used to provide practical physical stability to the amorphous systems (Vasconcelos et al., 2007). The inclusion of an additional polymer, however, selected based on its physiochemical properties, enables the design of more sophisticated delivery strategies with the amorphous drug in solid dispersion exhibiting a reduced particle size and lower thermodynamic barrier to dissolution (Verma and Rudraraju, 2014).

Several formulation approaches and manufacturing techniques to prepare ASDs containing poorly water soluble APIs have been introduced, for example spray drying (SD), hot melt extrusion (HME) and freeze drying (FD) (Douglas et al., 2015; Kumar et al., 2014; Cerdeira et al., 2013). Among these, spray drying is being more and more utilised to develop solid molecular dispersions of poorly soluble drugs (Hengsawas Surasarang et al., 2016; Sawicki et al., 2016) resulting in enhanced solubility and the development of sustained and targeted drug delivery systems.

Physicochemically, itraconazole (ITZ) can be categorised as a weak base, BCS class II compound with very poor water solubility of 1 ng/mL at neutral pH. The first oral dosage form of itraconazole was manufactured using a solid solution method in which the solvent based drug-polymer mixture was sprayed onto an inert sugar sphere in a closed Wurster process (Peeters et al., 2002). However, where most ASDs in the literature have been binary systems, comprising of drug and excipient polymer, reports have suggested that ternary ASD systems can have a stability advantage over binary (Six et al., 2004).

The aim of this project was to generate an optimised formulation comprising amorphous itraconazole and two excipient polymers in which the itraconazole was stable in the amorphous form over an extended period and which exhibited the capability to produce and maintain a supersaturation of itraconazole in acidic media.

* Corresponding author.
E-mail address: mark.davis@ul.ie (M.T. Davis).

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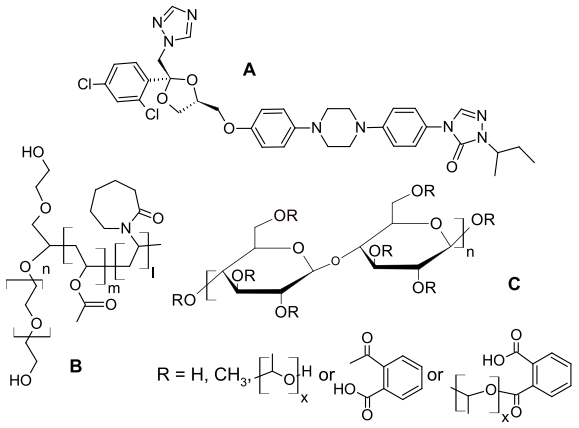

Fig. 1. Chemical structures of itraconazole (A), Soluplus (B) and HPMCP (C).

2. Materials and methods

2.1. Materials

Itraconazole (>99%) was purchased from Xi'an Lyphar Biotech Ltd. Accurate analytical standard of itraconazole (99.8%) for HPLC calibration was purchased from Sigma Aldrich. Polymers Soluplus and HPMCP HP-55 (HPMCP) were donated by BASF and Shin Etsu respectively. Solvents and chemicals were purchased from Sigma-Aldrich and were of HPLC and reagent grade.

2.2. Pre-formulation polymer and solvent selection test

In a typical experiment dichloromethane-methanol (1:1 v/v, 5 mL) was added to itraconazole (30 mg), Soluplus (30 mg) and HPMCP (40 mg) followed by vortex mixing (5 min) and visual inspection.

2.3. Design of experiments (DoE)

Design-Expert 9.0.6 software (Stat-Ease, Minneapolis) was utilised to generate a variety of 17 optimised formulations containing drug loads of 10–30% (Fig. 2 and Table 1). DoE has been employed to provide a methodical way of choosing the drug-polymer ratios.

2.4. Spray drying

A Büchi B-290 mini spray dryer was set up with a B-295 inert loop to enable the use of organic solvents and was connected to a condenser maintained at −20 °C and a high efficiency cyclone. A 0.7 mm 2-fluid pneumatic nozzle was fitted and the API – polymer solution was sprayed under a stream of nitrogen. Atomising nitrogen flowrate was ~473 L/h and the aspirator for the drying nitrogen was set to 100% (35 m3/h). The solution (0.5% w/v) of ITZ, Soluplus and HPMCP in dichloromethane – methanol (500 mL, 1:1 v/v) was pumped at 4 mL/min. Inlet temperature was set at 66 °C producing an outlet temperature of 40 ± 3 °C. All variables affecting the outcome of a spray drying experiment such as outlet temperature, solution concentration, aspirator rate, pumping speed were fixed between runs so that only formulation composition was varied. Powdered product was immediately analysed by PXRD and transferred to stability trial.

2.5. Stability studies

Ternary dispersions of ITZ were stored at (i) 20 °C/0% RH and (ii) 40 °C/75% RH using Amebis® stability pods and cabinets. The samples in the pods were monitored wirelessly by Amebis® software to ensure that temperature/relative humidity settings did not vary over time. Samples were removed for analysis at day 0, one month, three months and one year by PXRD. Other techniques mentioned directly below ascertained the stability of the powders after one year at these conditions.

2.6. Powder X-ray diffraction (PXRD) and small-angle X-ray scattering (SAXS)

A PANalytical Empyrean X-ray diffractometer attached to a computer running High Score Plus was used to collect and process X-ray data. Diffraction patterns were collected in-situ, by spinning powders on zero background discs within the X-ray beam. The radiation was generated by Cu filter at 40 kV and 40 mA. Data was collected over the 2θ range of 5–50°, with a step size of 0.026o and a step time of 56 s. Small-angle X-ray scattering (SAXS) was performed on a Philips XPERT Pro MPD diffractometer. Powders were spun on zero background discs within an X-ray beam generated by Cu filter at 40 kV and 40 mZ. Data was collected over the 2θ range of 1–10°, with a step size of 0.017o and a step time of 40 s.

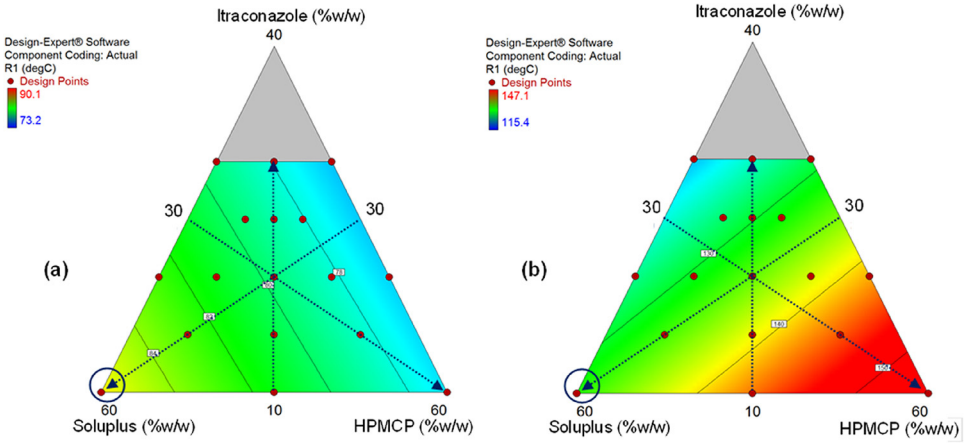

Fig. 2. A mixture (user-defined) design space with red dots indicating the 17 formulations. Circled point corresponds to a composition of 0.1 ITZ: 0.6 Soluplus: 0.3 HPMCP (Run 2 in Table 1). Plot fill colour indicates (a) T_{g1} and (b) T_{g2} value for the given formulation composition. Blue dotted arrows have been added as a reading aid for the three axes.