DESIGN OF SPRAY DRIED TERNARY SOLID DISPERSIONS
COMPRISING ITRACONAZOLE, SOLUPLUS AND HPMCP: EFFECT OF
CONSTITUENT COMPOSITIONS

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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.

KEYWORDS
Itraconazole, Soluplus, HPMCP, ternary, amorphous, spray drying

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.

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 (HPMC) 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% (Figure 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 0.026° 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 0.017° and a step time of 40 s.

2.7 Differential scanning calorimetry (DSC)

DSC studies were conducted on a PerkinElmer DSC 8500 equipped with a refrigerated cooling accessory (PerkinElmer, Workingham) using helium (30 mL/min) as the purge gas. The instrument was calibrated at heating rates of 100 and 200 °C / min using high purity indium and zinc to standardise the temperature and heat flow signals. Samples (2.0 – 5.0 mg) were weighed and placed in crimped DSC pans, then ramped from 0 - 180 °C at 100 °C / min to check for crystallinity or 200 °C / min to study the glass transition regions. Analysis was carried out using PE Pyris Thermal Analysis software, version 10.1 and any numerical values reported are the average ± SD of three independently prepared samples.

2.8 Solid state nuclear magnetic resonance spectroscopy (ssNMR)

13C solid state NMR spectra were recorded on a Bruker Avance III instrument operating with a 4 mm probe operating in double resonance mode. Samples were packed into 4 mm zirconia rotors and spun at 8 kHz at a magnetic field strength of 400.14 MHz for 1H and 100.61 MHz for 13C. The pulse sequence for 13C acquisition employed ramped cross-polarisation (CP) with a 70-100% ramp on the 1H channel and high power 1H decoupling with a SPINAL64 scheme. Magic angle spinning (MAS) was performed at 8000 Hz for all experiments and the 1H 90° pulse width was 3.1 µs. The CP contact time was 0.5 - 4 ms with recycle delays of 3 - 6 s depending on the T1 of the sample. A total of 1024 scans were averaged for each spectrum shown. 1H T1 (spin-lattice relaxation) were made using a 13C-detected saturation recovery pulse sequence, with 13 recovery delay slices ranging from 0.1 to 100 s. The magnetic field was adjusted such that the methylene peak of adamantane resonated at 38.48 ppm. Peak width was adjusted by setting the middle and fifth peaks of KBr to 128.29 and 134.14 respectively. Data was analysed using Bruker TopSpin 3.5 software.

2.9 Attenuated Total Reflection Fourier Transform Infra-red Spectroscopy

Molecular interactions between ITZ and the polymers were characterised using an FT-IR spectrometer equipped with a universal attenuated total reflection (ATR) accessory (PerkinElmer Spectrum 100). A small amount of each sample was placed in the ATR cell, and pressure was applied with a pressure arm. Scans were collected in the range of 4,000–650 cm−1 using the Spectrum software package (PerkinElmer, MA, USA).

2.10 Scanning electron microscopy (SEM)

Drug polymer formulations were attached to double sided carbon tape and sputter coated with a thin layer of gold followed by imaging using a Joel CarryScope JCM-5700 scanning electron microscope. Micrographs were recorded at 500, 2000 and 5000 times magnification, using a beam acceleration voltage of 5 kV, a spot size of 40 and a working distance of 12.

2.11 Supersaturated in vitro dissolution studies

The dissolution studies were carried out under non-sink conditions in glass bottles (100 mL) equipped with magnetic stirring bars (30 mm) rotating at 100 rpm. Glass vessels were charged with dissolution media (0.1 N HCl, 75 mL) at 37 ± 0.5 °C. A quantity of formulation or drug equivalent
to 37.5 ± 1 mg of ITZ (375 µg/mL, approximately 100 times the 0.1N equilibrium concentration solubility of 4 µg/mL), was weighed into a glass vial. The powder was pre-wetted with 2 mL of preheated HCl media using a Pasteur pipette and quantitatively washed into the dissolution media. During testing, samples (1.0 mL) were removed by syringe at 1, 2, 3, 4, 5, 6 and 24 h (without replacement) and immediately filtered (0.45 µm PTFE syringe filters) into HPLC vials already containing an equal volume of mobile phase (to minimise adsorption or crystallisation). Immediately after the second sample (2h), tribasic sodium phosphate (0.2M, 25 ± 1 mL) was added to give a neutral pH of 6.8 ± 0.1 using a calibrated pH meter, in accordance with USP guidelines for extended release dosage forms (Method A).

2.12 High performance liquid chromatography (HPLC)

Dissolution samples were analysed using an Agilent (Agilent, Little Island, Cork) 1260 Infinity II high performance liquid chromatography system, comprising of quaternary pump G1311B, diode array detector G1315D set at wavelength 263 nm, autosampler G1329B and thermostated column compartment G1316A set at 25.0 °C. The system was operated under isocratic flow at 1 mL/min using a mobile phase of acetonitrile:water:diethanolamine (69.95/30/0.05) equipped with a Phenomenex Luna 5 µm C18(2) 100 Å 150 mm x 4.6 mm (Phenomenex, Macclesfield, Cheshire) RP-HPLC column. Samples collected from the dissolution assay were injected in volumes of 20 µL. Data were collected and analysed using Agilent ChemStation software version C.01.07. Standards of ITZ (99.8% purity) were prepared in methanol from a stock solution of 1 mg/mL to quantify the levels of drug in the samples.

2.13 Particle size distribution (PSD)

A Microtrac S3500 series particle size analyser with tri-laser technology (Microtrac Inc., Montgomeryville, PA) was used to determine the particle size distribution of the samples. Dry measurements were carried out using air as the medium to convey the sample to the measuring cell.

3. RESULTS AND DISCUSSION

3.1 Polymer selection

The system was designed to contain two polymers with differing solubilities in aqueous media, similar to the system previously reported by Six and co-workers (Six et al., 2004). The dissolution of itraconazole is typically carried out in acidic media so one enteric and one non-enteric polymer were selected. Based on miniaturised solvent casting studies previously carried out in this group, Soluplus and HPMCP were selected (Davis et al., 2015). Soluplus is amphiphilic in nature and aqueous-soluble while HPMCP is insoluble in acidic aqueous conditions. Furthermore, Soluplus would be expected to exhibit a greater wettability and hydrophilicity than HPMCP (Zhong et al., 2016). The functional group chemistry of Soluplus includes H-bond acceptors caprolactam and acetate whilst the PEGylated region improves aqueous solubility (Figure 1). HPMCP contains phthalate which contributes to lowering the overall aqueous solubility, but imparts hydrogen-bond donation capability. Ternary formulation design is displayed in Figure 2.

This work involved spray drying and was run concurrently with an hot melt extrusion project in our group also studying ternary ITZ-Soluplus-HPMCP blends, so it was important that the selected polymers were suitable for both spray drying and hot melt extrusion. One of the advantages of spray drying is the ease with which excipients with differing properties can be incorporated, provided that a mutually appropriate solvent can be found. Hot melt extrusion, however, relies on excipients having suitable thermoplastic properties. Soluplus is suitable for processing by both hot melt extrusion and solvent evaporation (spray drying) methods while HPMCP, as a cellulosic polymer with a high Tg, can be difficult to extrude without the use of plasticisers (Karandikar et al., 2015).
HPMCP also has a proven record as a suitable polymer for the formulation of ITZ (Parikh et al., 2015). Lozanoc® (Mayne Pharma, Australia) has recently come to market in Australia and the EU and is a 40% dispersion of ITZ on 60% HPMCP HP-50. In our studies of these systems, we have found that the inclusion of Soluplus with HPMCP has led to ease of processing by hot melt extrusion and contributes to higher drug concentrations in acidic media.

### 3.2 Spray Drying

A solubility screening step was introduced prior to spray drying to ensure that the three components were in solution to aid production of a homogenous product. After a range of permutations, dichloromethane-methanol (1:1) was selected as the solvent as it was capable of completely dissolving all three components at the required loading. The spray dried product was a white, fluffy powder which, following inspection using SEM, was shown to be comprised of particles with a collapsed or dimpled shape. The development of particles of this nature with an uneven surface has been associated with the spray drying of solutions with a Peclet number greater than 1 which causes regions of high viscosity to develop on the surface of the particles during drying and which is typical of solutions containing polymers (Vehring, 2008)(Bittner and Kissel, 1999). The resultant powders from each run were also analysed by Microtrac particle size analysis.

The cumulative diameters of the powdered products ranged from D10 0.681 µm (ASD 8) to 0.782 µm (ASD 3); D50 1.51 µm (ASD 8) to 2.37 µm (ASD 3) and D95 13.5 µm (ASD 11) to 244.4 µm (ASD 17). In general the majority of the particles fell into the size range 1-10 µm and the presence of particles a number of orders larger than this was attributed to particle agglomeration during drying and storage.

### 3.3 PXRD and SAXS

Each of the produced spray dried formulations were immediately analysed by PXRD on Day 0. The powders were then filled into vials and transferred to a desiccator at 20 °C / 0% RH and to Amebis® stability pods in controlled ovens at 40 °C / 75% RH. Over the following year, samples were removed for PXRD analysis at weeks 2, 4, 8, 12, 16, 48 and 52. The test is used to mimic shelf-life storage stability of pharmaceutical formulations. For all samples at each time point no Bragg peaks were detected and from this it was concluded that all formulations were PXRD amorphous (Figure 3). The sensitivity of the PXRD method was confirmed separately with a spray dried powdered formulation of itraconazole-HPMCAS-Soluplus (20:40:40) which was PXRD amorphous at day 0, but from which the characteristic Braggs peaks of ITZ could be observed following four weeks of storage.

SAXS was performed after one year of storage following a recent report of liquid crystalline phases of itraconazole from Tajber and co-workers (Mugheirbi and Tajber, 2015). The technique was used to detect any short range order indicative of a liquid crystalline phase which might not be detected by standard PXRD. None of the formulations showed any trace of this short range liquid crystalline character.

### 3.4 DSC

Through the use of the Perkin Elmer DSC8500 it was possible to explore the use of much faster heating rates than are used during standard DSC. In increasing heating rate the sensitivity of the DSC is also increased and thus smaller transitional changes can be detected beyond the threshold of instrumental noise (Craig and Reading, 2006). This analysis method was therefore utilised as one which might give better sensitivity to any crystallinity contained in the formulations. All of the samples from the stability study were tested i.e. from the desiccator and from the Amebis® system at 40 °C / 75% RH and even using this increased sensitivity analysis method the absence of any
melt exotherm around the melting point of the API (168.7 ± 0.3 °C measured using a heating rate of 100 °C/min) was confirmed (Figure 4).

The difficulty in measuring the glass transition event in celluloses is well known (McPhillips et al., 1999) so having the capability to probe the thermal glass transition region using increased heating rates was advantageous. A disadvantage associated with increasing the heating rate in DSC is the decreased resolution of thermal events. Two peaks which may be fully resolved at a slower heating rate can merge together when heated more quickly. For this reason 100 °C / min was determined to be the optimum heating rate for the detection of crystalline material around the melting point of the API, however to better detect the weak \( T_g \) of HPMC 200 °C / min was used.

At this heating rate the measured \( T_g \) of ITZ, Soluplus and HPMC is 59.0 ± 0.9, 82.1 ± 2.2 and 147.6 ± 1.5 °C (all n = 3) respectively. Van den Mooter and co-workers claimed that the anti-plasticising effect of the polymer, rather than intermolecular interactions, was the only relevant factor (Van den Mooter et al., 2001) contributing to system stability. HPMC has a greater stabilising influence on ITZ than Soluplus either through its propensity to hydrogen bond with ITZ or due its higher \( T_g \).

The Couchman-Karasz equation for ternary systems (Equation 1) can be used to predict the value of the glass transition temperature(s) of such systems (Levine, 2002). The equation is based on classical thermodynamics theory with an assumption that the system is purely conformational where \( x_i \) refers to the mass fraction of component \( i \), \( \Delta C_{pi} \) is the change in heat capacity of component \( i \) between its liquid-like and glassy states. For polymer blends of three components the subscript 1 refers to HPMC, subscript 2 to Soluplus and 3 refers to the component of lowest \( T_g \), in this case ITZ.

\[
T_g = \frac{x_1 \Delta C_{p_1} T_{g_1} + x_2 \Delta C_{p_2} T_{g_2} + x_3 \Delta C_{p_3} T_{g_3}}{x_1 \Delta C_{p_1} + x_2 \Delta C_{p_2} + x_3 \Delta C_{p_3}} \tag{1}
\]

Due to the complexity of the ternary systems, the assumption of ideal mixing incorporated into the Couchman-Karasz equation may not be applicable; nevertheless, the values produced from the equation generally fell near to the halfway point between the two present values. The forces behind such a separation are unclear, but may be due to polarity and conformational flexibility issues. In any case, the stability against crystallisation of the ternary systems was excellent and the solubility was greatly increased compared to the crystalline drug and these outcomes were considered to be the most important, although a single homogenous formulation would be preferred.
3.5 DOE RESULTS

The factors measured were the weight percents (% w/w) of formulation ingredients; factor A: ITZ, factor B: Soluplus, and factor C: HPMCP and their percent amounts sum to 100%. The limits for the percent amounts of ITZ 10% \( \leq A \leq 30\% \) and Soluplus and HPMCP 30% \( \leq B/C \leq 60\% \). Two responses were recorded, namely the value of the two measured \( T_g \)s (\( T_{g1} \) and \( T_{g2} \) in Table 1), and analysis of data was carried out using two separate ANOVA; one for each response. A graphical representation of the results for the two models is shown in Figure 2.

On the basis of comparison of statistical indices for model adequacy, a *Linear Mixture model* was selected for both responses as shown in Eq (2) and Eq (3) below:

Final equation for \( T_{g1} \) in terms of real components

\[
T_{g1}=+65.48980 \times \text{ITZ}+97.96599 \times \text{Soluplus}+68.48028 \times \text{HPMCP} \]  \[\text{(2)}\]

Final equation for \( T_{g2} \) in terms of real components

\[
T_{g2}=+60.62902 \times \text{ITZ}+115.66711 \times \text{Soluplus}+189.72426 \times \text{HPMCP} \]  \[\text{(3)}\]

Values of "Prob > F" less than 0.0500 indicate model terms are significant. Model 1 exhibited a model F-value of 3.1 and a "Prob > F" of 0.0411 while the similar values for model 2 were 26.78 and 0.0001, implying that both models are significant. There is only a 4.11% or 0.01% (model 1 and 2 respectively) chance that F-values this large could occur due to noise. In both cases A, B and C terms are significant model terms.

From Figure 2a it is observed that \( T_{g1} \) increases with increasing Soluplus content. This observation is in agreement with the characterisation of these formulations as containing a Soluplus-rich and an HPMCP-rich amorphous phase. Therefore as the amount of Soluplus in the formulation increases, the ratio of Soluplus to ITZ in the Soluplus-rich phase increases, thus causing an increased overall \( T_g \) due to the higher \( T_g \) of the polymer in comparison to the API. From Figure 2b it is observed that as HPMCP content increases, \( T_{g2} \) is increased. There is, however, a difference in the gradient of the contour lines between the two models. For model 1 ITZ and HPMCP are given similar weighting in the calculation of \( T_{g1} \), with the contour lines orthogonal to the Soluplus axis. Conversely for model 2, the contour lines are shifted toward Soluplus, suggesting a change in the contribution of Soluplus to \( T_{g2} \) depending on HPMCP content and a possible limit to the miscibility of Soluplus in the ITZ-HPMCP system.

3.6 FTIR and ssNMR

The FTIR spectra for the formulations prepared in this study and the individual components are presented in Figure 5. At 898 cm\(^{-1}\) a peak was observed in the crystalline sample of ITZ only. The peak was not present in the amorphous sample of ITZ (prepared by melt quench), in any of the formulations or the polymers. 898 cm\(^{-1}\) is most likely due to an aromatic C-H out-of-plane bending vibration. ATR-FTIR represents a rapid test method for qualitatively determining the presence or absence of crystalline ITZ with minimal sample preparation time.

The impact of hydrogen-bonding in amorphous dispersion stability has been well documented (Vasanthavada et al., 2005). ITZ cannot self-associate through H-bonding, as it contains only donor functional groups, however it can H-bond to HPMCP and may form other associations with Soluplus. Soluplus cannot self-associate as it contains only acceptors, but can H-bond with HPMCP. HPMCP can associate with itself, the drug and Soluplus as it contains both acceptors and donors. The phthalate functional group is able to associate favourably with the ITZ aromatic rings.
through $\pi-\pi$ interactions. Conformational flexibility of the components will be limited by rotational degrees of freedom around individual bonds reducing the number of possible interactions. For instance, HPMCP will be limited in flexibility due to the preferred orientation of the glucopyranose rings.

Solid state NMR spectra were recorded of ASD 16 (containing 30% drug load, 40% Soluplus and 30% HPMCP) after one year of storage in a desiccator (Figure 6). The data compared well with that previously reported (Van Eerdenbrugh et al., 2009)(Song et al., 2015). Broadening of the peaks in ASD 16 relative to crystalline ITZ indicated that the drug was in the amorphous form. ssNMR also provides additional structural information confirming that the drug was also chemically intact and had not oxidised or otherwise degraded.

3.7 Dissolution studies

HPLC analysis was performed rather than UV assay to ensure that absorbance was due to analyte (ITZ) rather than impurities or polymer (e.g. phthalate groups). The retention time of ITZ was approximately 9.3 min with consistent reproducibility and no unexplained peaks or baseline drift were encountered. All analytical tests maintained system suitability limits for linearity from 0.100 to 100 $\mu$g/mL ($r^2 \geq 0.999$) and reproducibility of replicate injections (% RSD < 0.3%). Sharp single peaks at expected $R_f$ values confirmed lack of chemical or bacterial degradation during the one year stability test. The method was based on that previously reported by DiNunzio (DiNunzio et al., 2008). Diethanolamine was added to the mobile to ensure that only deprotonated ITZ (pKa = 3.7) was present. The limit of detection of was 100 ng/mL.

Dissolution studies were operated under supersaturated, non-sink, in vitro conditions using USP II method for enteric coated formulations adapted to use a magnetic stirring bar (DiNunzio et al., 2008). The relative dissolution ability of the 17 blends and relationship to the formulation was of interest. Data for the highest, middle and lowest concentrations is displayed in Figure 7. A comparison of formulation, dissolution and particle size reveals that formulations richer in Soluplus generally had a lower D50 particle size distribution and a higher solubility. Formulations richer in HPMCP generally had higher D50 particle size distribution and had lower solubility (Figure 9). The reason for the larger PSD is most likely because HPMCP has a much greater effect on viscosity than Soluplus or ITZ. When viscosity is higher droplet formation is more difficult so larger droplets are formed (Vehring, 2008). The most favourable concentrations after 2 h were from formulations containing the following component ranges: 10-20% ITZ, 37.5-50% Soluplus and 35-45% HPMCP.

4. CONCLUSIONS

It has been shown that a compositional range of ternary ASDs of ITZ, HPMCP and Soluplus are extremely stable, remaining amorphous for one year at 40 °C and 75% RH, as confirmed by a range of techniques; PXRD, SAXS, DSC, FTIR and ssNMR. The formulation with the highest Soluplus content (60% w/w) and lowest drug content (10% w/w) maintained a homogeneous single amorphous phase over one year while all others were shown to contain Soluplus-rich and HPMCP-rich phases. Following spray drying those formulations with greater Soluplus content generally had lower particle size distributions than those containing more HPMCP. Similarly, formulations with higher Soluplus levels generally exhibited a greater initial rate and extent of dissolution than those with higher HPMCP content.

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REFERENCES


Figure 1: Chemical structures of itraconazole (A), Soluplus (B) and HPMCP (C)

R = H, CH₃, or

Figure 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
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.

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<th>Soluplus (%)</th>
<th>HPMCP (%)</th>
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<th>$T_{g2}$ (°C)</th>
<th>[ITZ] (µg/mL)</th>
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<tr>
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<td>79.4</td>
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Table 1: ASD formulation code, composition (% w/w), values of glass transition temperatures (°C) and drug concentration (µg / mL) after 2 h in acidic dissolution media.
Figure 3: PXRD traces from analysis of ASD 14 (ITZ 25%, Soluplus 35% & HPMCP 40%) showing amorphous halo at
Day 0 and weeks 2 to 50. Other ASD gave similar PXRD results.
Figure 4: DSC thermograms of ASD 1 - 17 following storage at 40 °C / 75% RH for 1 year. Crystalline ITZ is included, melting from 161 - 182 °C. The melt peak did not appear in any of the 17 formulae, confirming that the amorphous form is very stable.

Figure 5: ATR-FTIR spectra of crystalline ITZ, amorphous ITZ, Soluplus, HPMCP and ASD 1 - 17. The peak at 898 cm\(^{-1}\) was attributed to an aromatic C-H out-of-plane bending vibration and was detected only in crystalline ITZ, but not...
in ASD 1 - 17, indicating that the drug was amorphous in every formulation.

Figure 6: $^{13}$C-CPMAS ssNMR spectra of Soluplus, HPMCP, crystalline ITZ and ASD 16 (after 1 year of storage). Broadened ITZ peaks demonstrated that the drug was physically amorphous and chemically intact.
Figure 7: Non-sink, supersaturated, in vitro dissolution studies using the FDA method recommended for enteric formulations. ASD 7, 15 and 16 represented the high, middle and low values within the 17 formulations and crystalline ITZ was included for comparison. Samples were removed at 1, 2, 3, 4, 5, 6 and 24 h and analysed directly by HPLC. Crystalline ITZ released 4 µg / mL after 1 h, but was below the limit of detection (100 ng / mL) post neutralisation, due to precipitation. Release of drug post neutralisation was low but higher values were found in formulations with higher levels of HPMCP.

Figure 8: Concentration values for ITZ ASD 1-17 and crystalline ITZ following 2 h dissolution in acidic media with non-sink conditions. Each ASD achieved a greatly superior concentration to crystalline ITZ, up to 50 times higher in the best case. The concentration values varied according to formulation composition with lowest and highest values of 127 (ASD 16) and 203 µg / mL ITZ (ASD 7) respectively.
Figure 9: The relationship between particle size distribution (PSD) D50 values and formulation composition by quantity of HPMCP and Soluplus used (expressed as mg of polymer out of a 2.500 g formulation total mass). An increase in HPMCP concentration generally led to higher D50 values whilst an increase in Soluplus D50 values generally led to lower D50 values.