Continuous Manufacture and Monitoring of Itraconazole Amorphous Solid Dispersions by Hot Melt Extrusion using In-Line UV-Vis Spectroscopy

Hetvi Triboandas

Leicester School of Pharmacy, De Montfort University, Leicester
p14169329@alumni365.dmu.ac.uk

10th APS International PharmSci Conference
Greenwich 2019

DE MONTFORT UNIVERSITY LEICESTER

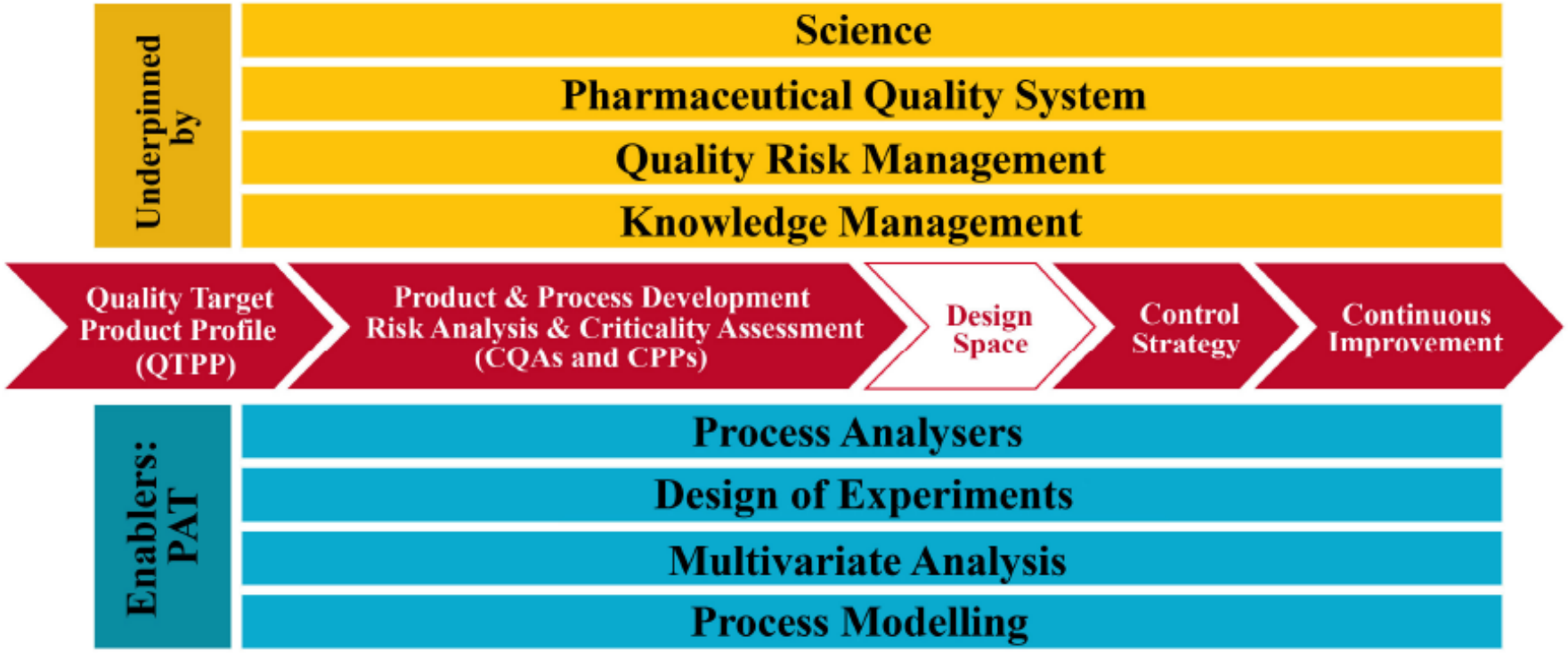
Outline

- Quality by Design (QbD) Approach
- Continuous Processing and in-line Monitoring
- QbD Methodology
  - QTPP
  - Risk Assessment
  - DoE
  - Modelling
- Results
  - In-line multivariate UV-Vis functional principle component analysis (FPCA)
  - XRD and DSc
- Conclusions

QbD Approach

Quality by Design (QbD) Approach

- "A systematic approach to development that begins with predefined objectives and emphasizes product and process understanding and process control, based on sound science and quality risk management" [1].
- The QbD principles as defined by the ICH Q8 underpin the current study.



The QbD flow [2]

[1] ICH Harmonised Tripartite Guidelines, "Pharmaceutical development Q8 (R2)", 2004, Available at: https://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Quality/Q8_R1/Step4/Q8_R2_Guideline.pdf, [Accessed 3/9/19].

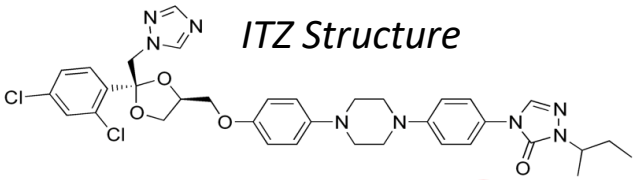
[2] W. Schlindwein, M. Gibson, "Pharmaceutical Quality by Design: A Practical Approach", John Wiley & Sons, London, 2018.

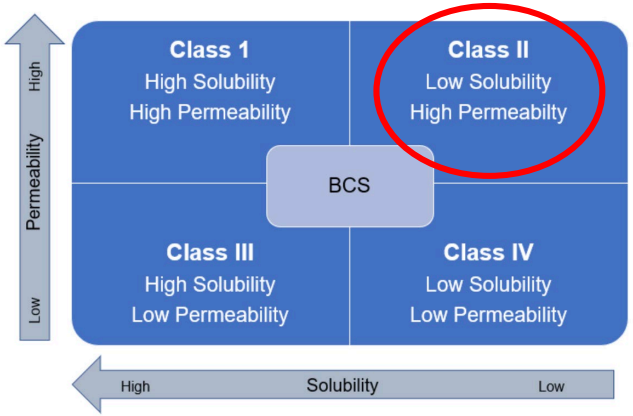
Continuous Processing and in-line monitoring

- Hot melt extrusion (HME) was used to produce amorphous solid dispersions (ASDs) of itraconazole (ITZ) in kollidon®VA64.
- ITZ is a common antifungal drug and is a BCS Class II drug.
- In–line UV-Vis spectroscopy was used to continuously monitor the process; a process analytical technology (PAT) tool.
- Within the extruder the raw materials are conveyed in a heated barrel, melted and mixed by rotating screws. The resultant melt is then forced through a die to form extrudates.

HME process equipment

ITZ Structure

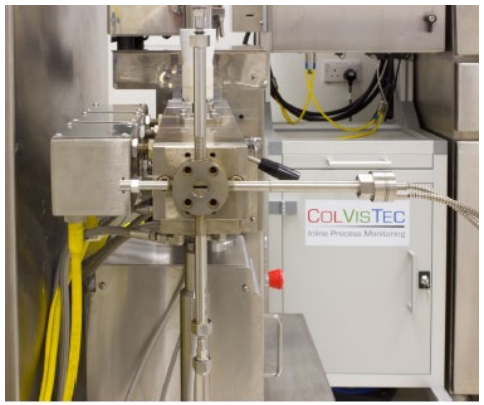


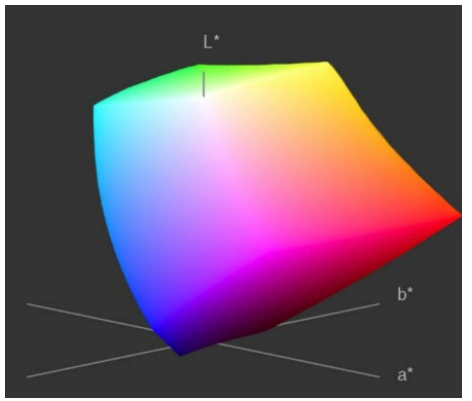


HME barrel with twin screws

Continuous Processing and in-line Monitoring

PAT "A system for designing, analysing, and controlling manufacturing through timely measurements (i.e. during processing) of critical quality and performance attributes of raw and in-process materials and processes, with the goal of ensuring final product quality'' [3].





In-line UV-Vis Spectroscopy

Absorbance (%)

- Measure API solubility
- Able to determine the API concentration

Colour (%)

- Measure for appearance
- Coded using the CIE L*(Lightness), b*(Yellow-Blue) and a*(Red- Green) [4].

[3] FDA Guidance for Industry, "PAT – A Framework for Innovative Pharmaceutical Development, Manufacturing and Quality Assurance", 2004; Available at: https://www.fda.gov/downloads/drugs/guidances/ucm070305.pdf, [Accessed 3/09/19].
[4] G, Hoffman, "CIELab Color Space", 2003, Available at: http://docs hoffmann.de/cielab03022003.pdf [Accessed 3/09/19].

QbD Methodology

- QTPP

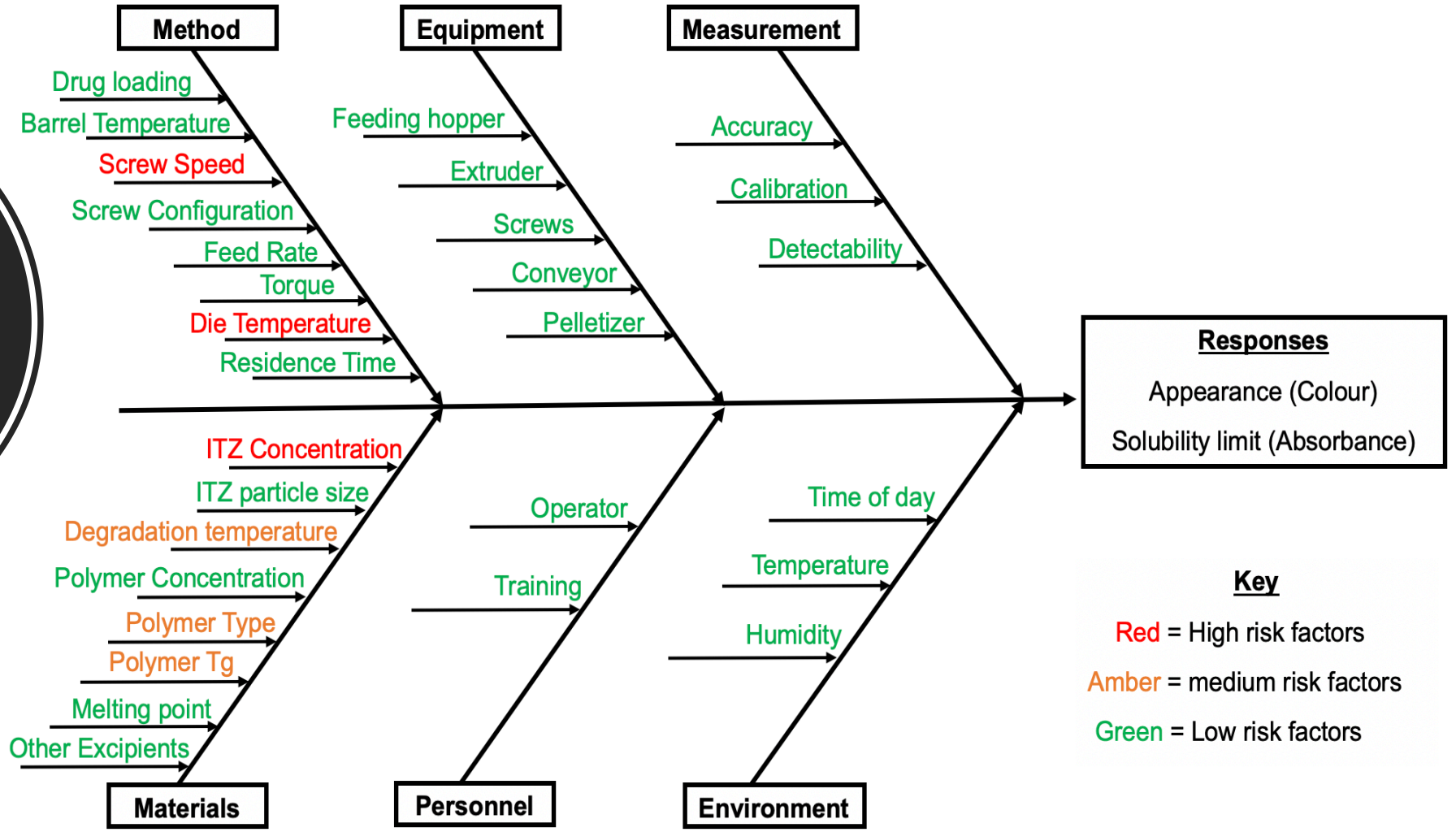
- The QTPP was defined for an intermediate ASD

Product Quality Attribute	Quality target	Potentially Critical?
Dosage form	ASD	Yes
Appearance	Uniform colour	Yes
Identity	Positive for itraconazole	Yes
Moisture content	low	Yes
Content Uniformity	Meets Pharmacopoeia acceptance criteria	Yes
Particle Size Distribution	Uniform	Yes
Crystallinity	None	Yes
Solubility	Below saturation	Yes
Stability	2 years at 25 °C / 60°C RH	Yes

QbD Methodology

- Risk Assessment

- The **preliminary risk assessment (RA)** conducted is shown below.
- The **CQAs** were appearance (colour) and solubility (absorbance).
- The **CPPs** were die temperature, screw speed and ITZ concentration.

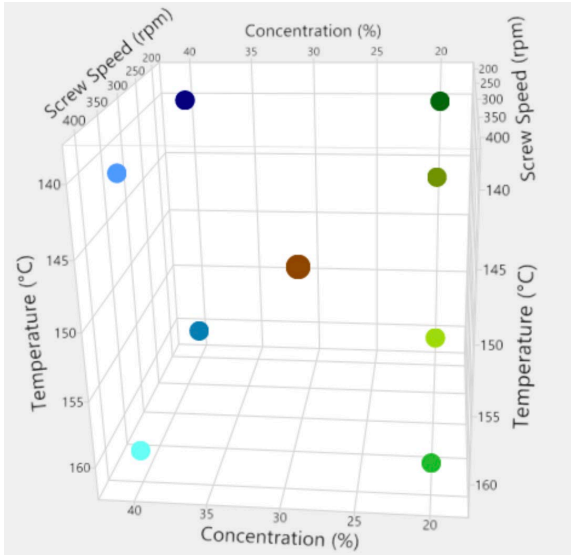


QbD Methodology

- DoE

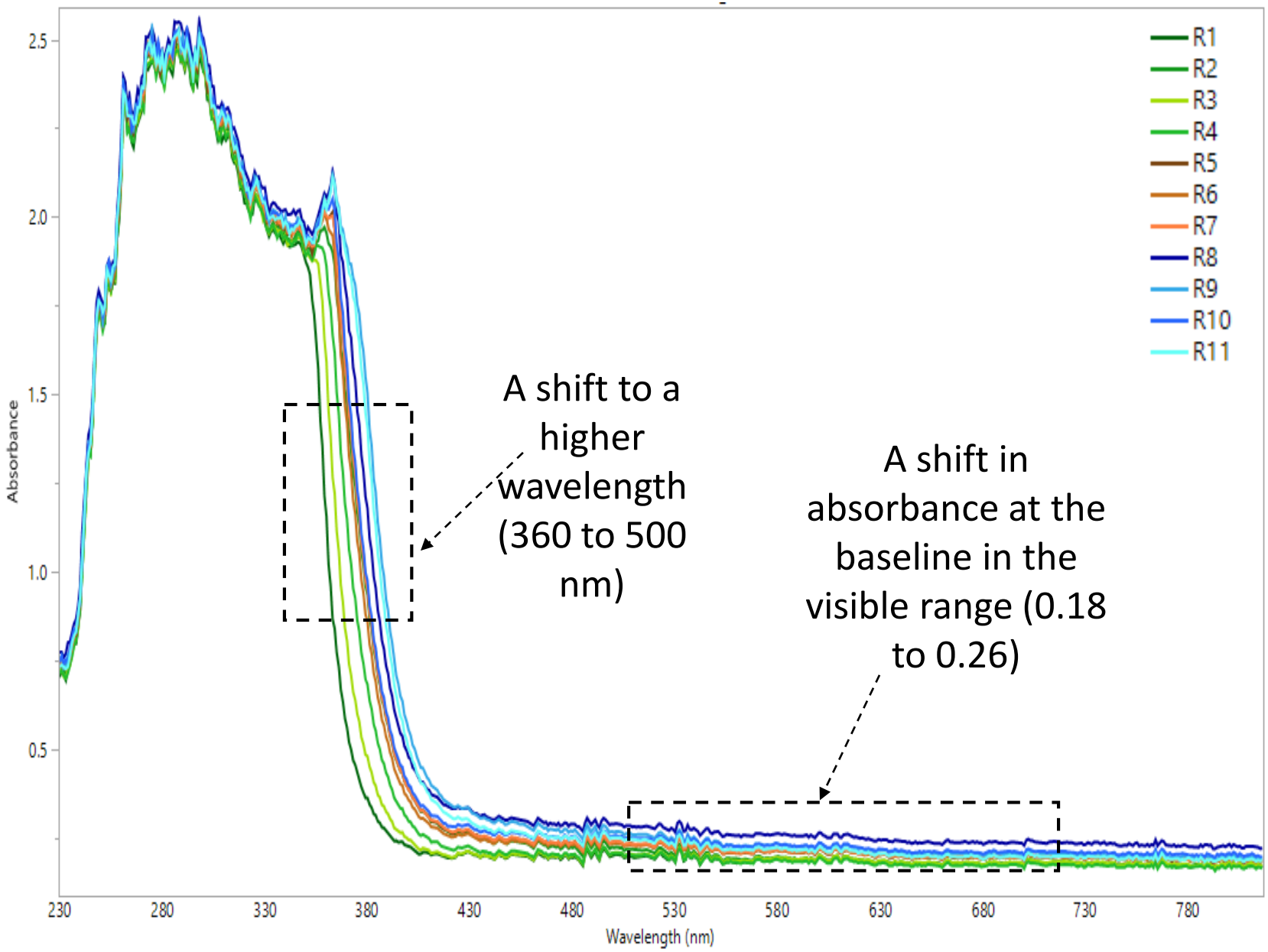
- A 2^3 full factorial screening design was adopted, with 11 runs in total, including 3 centre points.

Run (R)	Screw Speed (rpm)	Temperature of die (°C)	Concentration of ITZ in KVA64 (% W/W)
1	200	140	20
2	400	140	20
3	200	160	20
4	400	160	20
5	300	150	30
6	300	150	30
7	300	150	30
8	200	140	40
9	400	140	40
10	200	160	40
11	400	160	40



3D Scatterplot for the DoE

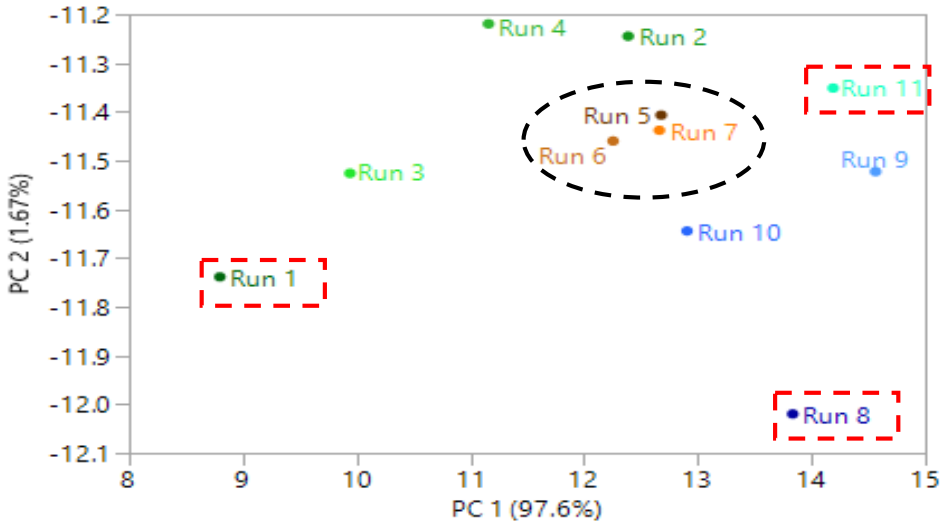
In-Line UV-Vis Results



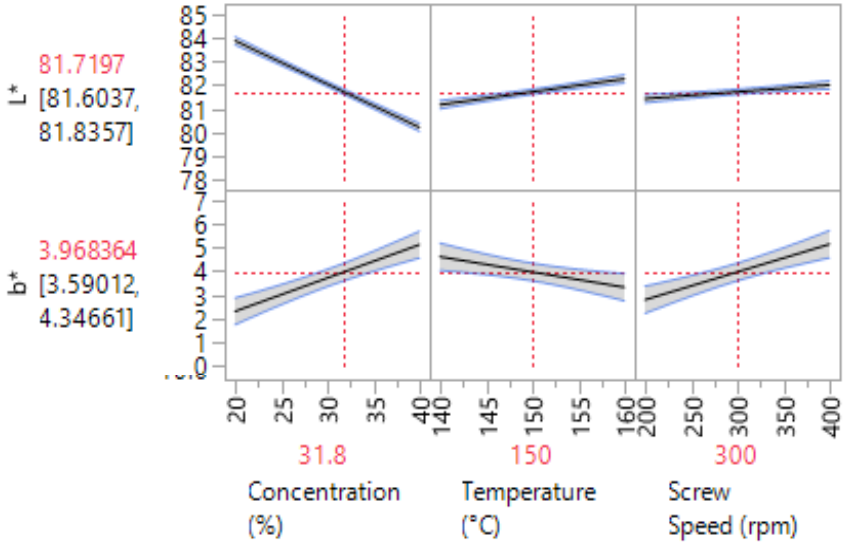
FPCA Results

- FPCA results showed that the score of **PC1**, accounted for **97.6%** of the variation and **PC2** accounted for only **1.67 %** of the variation.
- The score plot demonstrated that the difference in **R1** and **R8** can be explained using **PC1** and the difference between **R8** and **R11** can be explained using **PC2**.
- The prediction profiler shows that the concentration of ITZ had the biggest effect on the L* and b*.

The Score plot



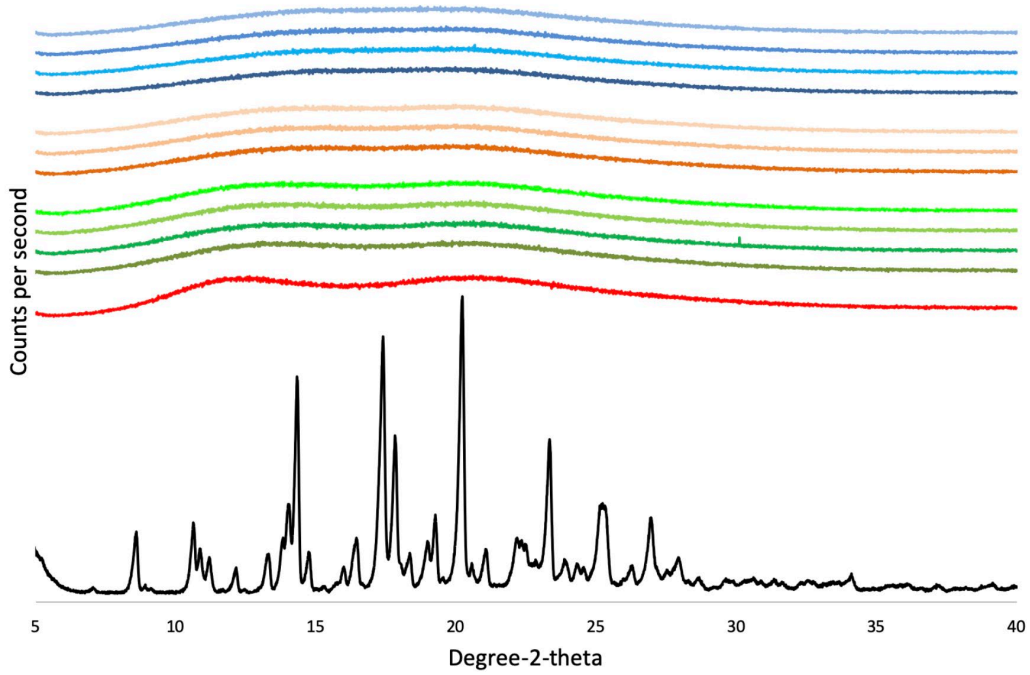
The Prediction profiler



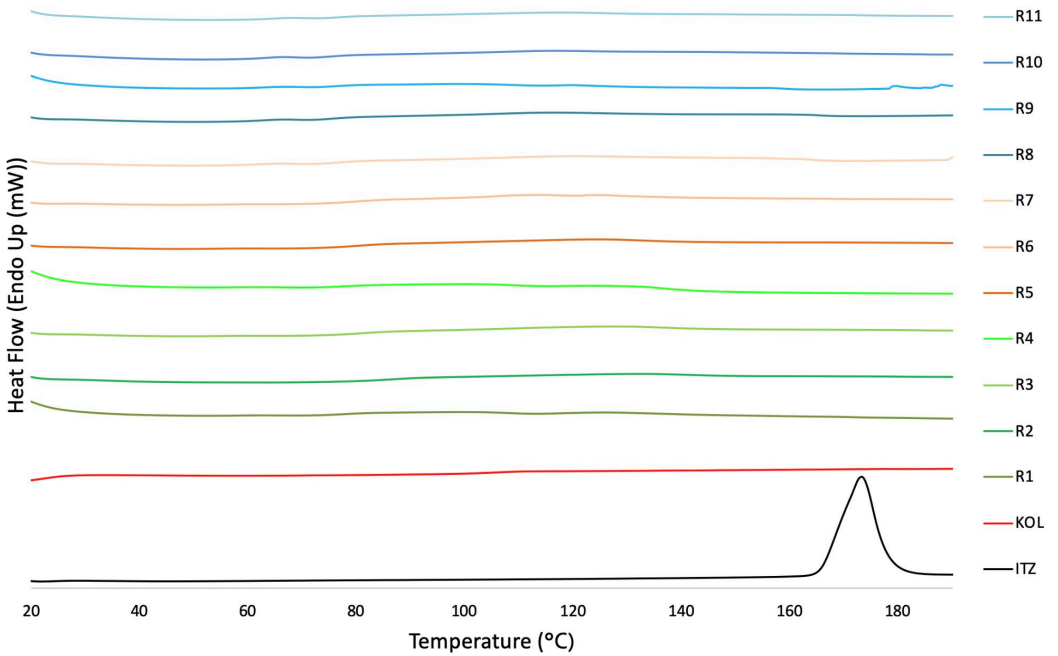
XRD and DSc results

- All extrudates were found to be amorphous.
- In the XRD results, characteristic peaks of ITZ were not observed in all the extrudates.
- For the DSc results, there was an absence of the ITZ melting peak at 173°C in all the extrudates produced.

XRD Results



DSc Results



Conclusions

- QbD methodology was applied to develop ASDs of ITZ.
- All the samples produced using the DoE conditions were amorphous which was confirmed by the DSc and XRD results.
- In-line UV-Vis enabled the process to be continuously monitored.
- FPCA was a powerful tool to analyse the full UV-Vis spectra and show the effects of oversaturation on the absorbance using multivariate analysis.
- In general, concentration was found to be the main factor affecting the responses measured.
- Further optimisation studies need to be conducted to propose and verify the design space.

Acknowledgements

- Dr Walkiria Schlindwein
- Mariana Bezerra
- Juan Almeida
- Martin Owen

Thank you for your attention