CMAC FUTURE MANUFACTURING RESEARCH HUB

Developing process understanding for continuous manufacturing of Lamivudine (Epivir®) Stable Form I

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Background

Why the considerations for Lamivudine?

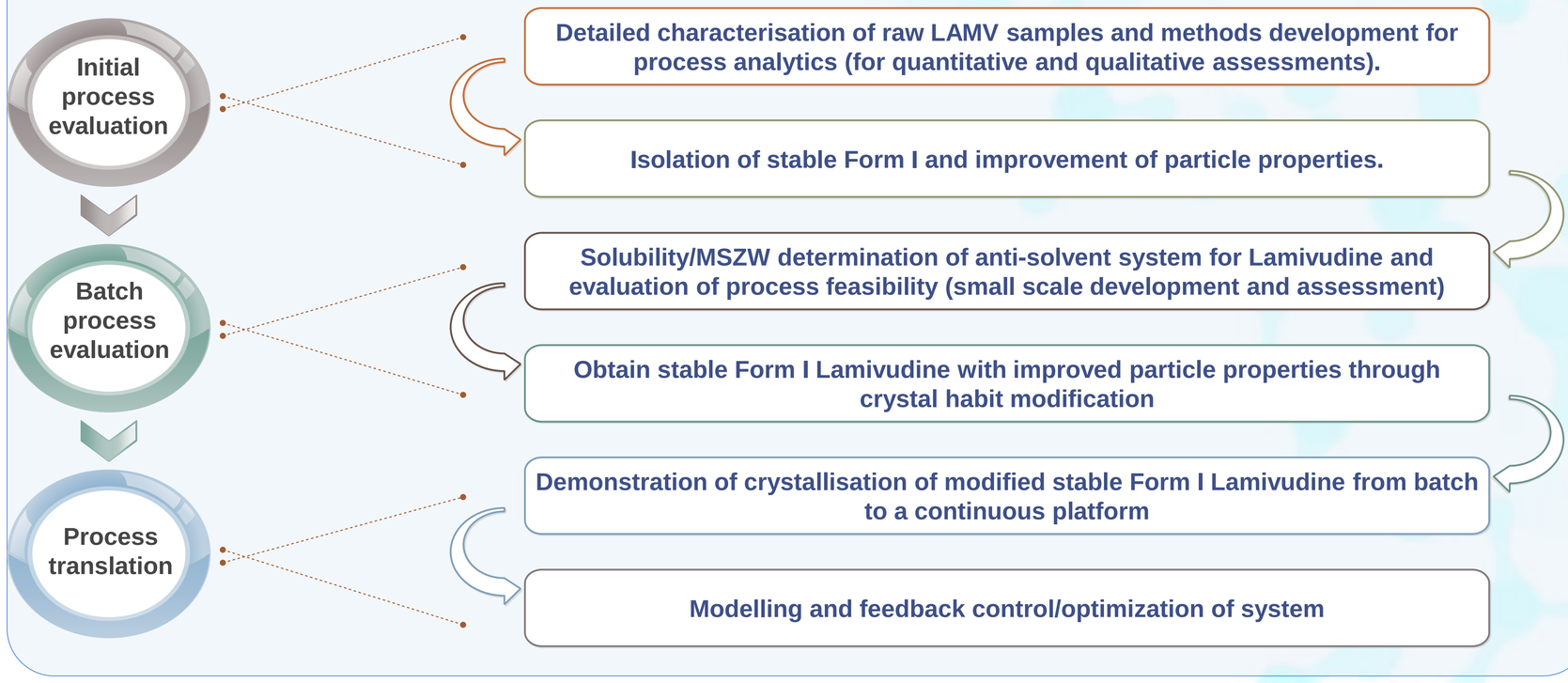
- Increasing numbers of HIV/AIDS infections on yearly basis (2.1 million new cases in 2015, UNAIDS)
- Hepatitis B infections (257 million cases globally, WHO)
- Currently FDA-approved antiretroviral therapy for the prevention and treatment of both viral infections (FDA).

Key research considerations and interests

To the best of our knowledge, no publication yet exists on continuous manufacturing of stable Lamivudine form 1. The key research question here is:

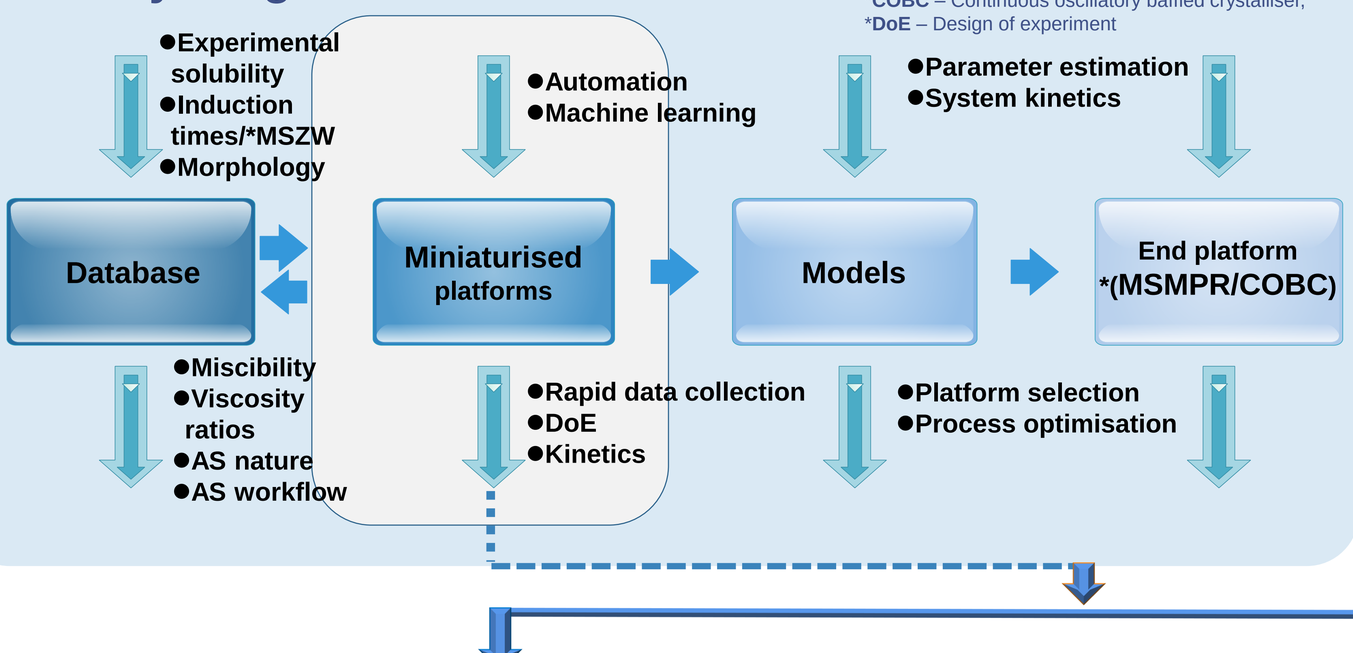
- ***Translate current batch crystallisation into a continuous process?***
- ***Improve the downstream process-ability by modifying the particle properties?***
- ***Develop miniaturise platforms for accelerated process development?***

Objectives

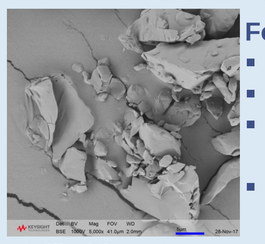


Early Stage Process Workflow

*MSZW – Metastable zone width, *AS - Antisolvent
*MSMPR – Mixed-suspension, mixed-product removal
*COBC – Continuous oscillatory baffled crystalliser,
*DoE – Design of experiment

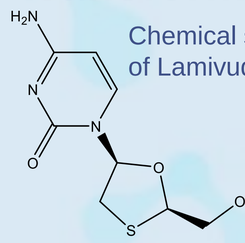


Lamivudine Morphology and Transformation



Milled form II raw material

Form II
- Anhydrous
- Bi-pyramidal
- Thermodynamically favoured form
- Formed in anhydrous solvents



Chemical structure of Lamivudine

Recrystallised form I from raw material

Form I
- 0.2 Hydrate
- Needle-like
- Marketed API (Epivir®)
- Unstable under mechanical action
- Requires water activity of ~ 5 - 20%

Recrystallised form I wet product from cooling crystallisation

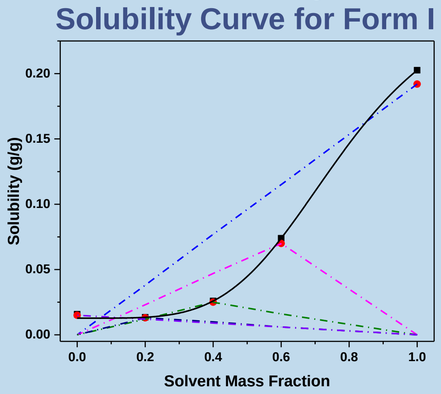
Solvents Screening

Experimental Approach

Miniaturised parallel screening platform → **15 vials with maximum of 8 mL working volume**

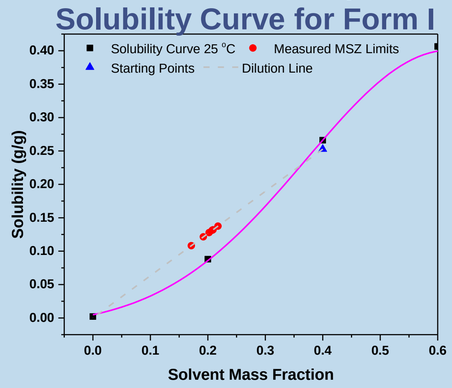
Experimental set-up

DMF/Acetone System Solubility Curve for Form I



- As with the solubility curve it can be seen from the supersaturation profiles that the addition of antisolvent drives the system into a significantly supersaturated state.
- With a maximum possible supersaturation of ~3.5 and a maximum predicted yield of ~75%, this system is suitable for antisolvent crystallisation.
- Might need to consider water activity for form control.

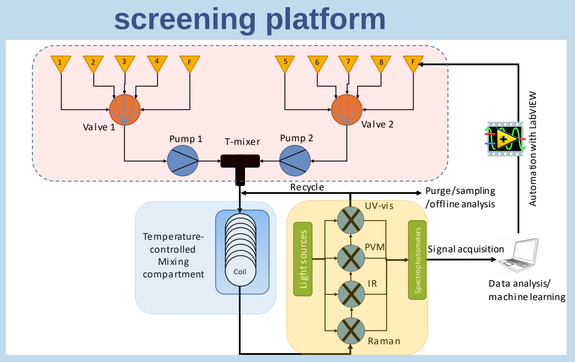
Water/Acetonitrile System Solubility Curve for Form I



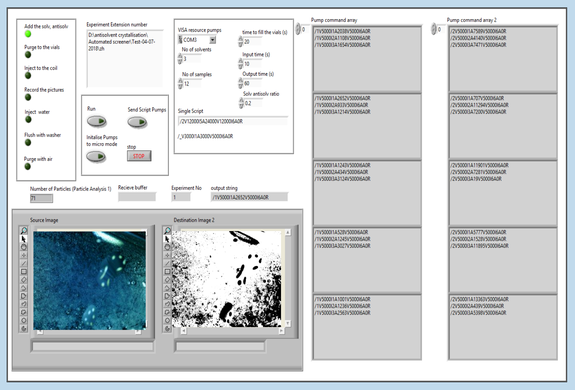
- Only solutions prepared at starting points of 0.6 and 0.4 solvent mass fractions can be driven into a supersaturated state by the addition of Acetonitrile.
- Highest achievable supersaturation: ~1.5. Maximum projected yield: ~32%
- This means that the yield of the isothermal anti-solvent crystallisation in this system is ~40% lower than a cooling crystallisation

Novel Miniature Platform Development for Morphology Optimisation

Miniaturised autonomous screening platform

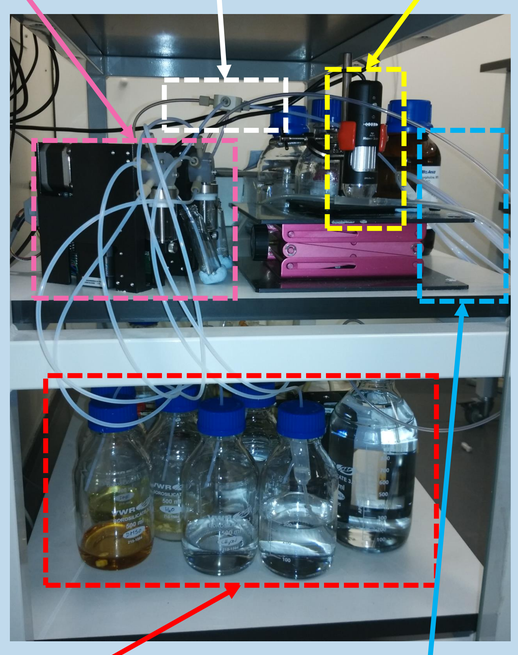


The feedback relation between the modules of the platform including temperature and flow control and the image processing.



LabVIEW front panel ensuring the automatic control and monitoring of the platform.

Feedback control → **Automation & visualization**



Conclusions

- Metastable zone width of the binary mixtures identified for the two solvents screening.
- A miniature platform was developed for morphology screening and incorporation of the feedback control to optimize the shape and size of Lamivudine crystals.

Future work

- Screening of potential solvent pairs suitable for developing continuous antisolvent crystallisation.
- The developed novel platform will be applied for morphology screening and incorporation of the feedback control to optimize the shape and size of Lamivudine crystals.

References

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Acknowledgments

This work is carried out as a part-time team project by the Industrial Research Associates and funded by TIER 1 industry partners. Contributions of Cameron Brown and all the Hub technicians are duly acknowledged.