

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

Detailed characterisation of raw LAMV samples and methods development for process analytics (for quantitative and qualitative assessments).

Isolation of stable Form I and improvement of particle properties.

Solubility/MSZW determination of anti-solvent system for Lamivudine and evaluation of process feasibility (small scale development and assessment)

Obtain stable Form I Lamivudine with improved particle properties through crystal habit modification

Demonstration of crystallisation of modified stable Form I Lamivudine from batch to a continuous platform

Modelling and feedback control/optimization of system

*MSZW - Metastable zone width, *AS - Antisolvent **Early Stage Process Workflow** *MSMPR - Mixed-suspension, mixed-product removal *COBC - Continuous oscillatory baffled crystalliser, *DoE – Design of experiment Experimental Parameter estimation solubility Automation System kinetics Induction Machine learning times/*MSZW Morphology **End platform Miniaturised** Models **Database** *(MSMPR/COBC) platforms Miscibility Rapid data collection Platform selection Viscosity ●DoE Process optimisation ratios Kinetics AS nature

Lamivudine Morphology and Transformation Form II Chemical structure



material Form I 0.2 Hydrate Needle-like Marketed API (Epivir®)

Unstable under mechanical action Requires water activity of ~ 5 - 20% Recrystallised form

from raw material

Recrystallised form I wet product from cooling crystallisation

Solvents Screening

Experimental Approach Miniaturised parallel screening platform

(b) (0.15)

5 0.10 -

DMF/Acetone System

Solubility Curve for Form I

AS workflow

15 vials with maximum of 8 mL working volume



Initial

process

evaluation

Batch

process

evaluation

Process

translation

Experimental set-up

- 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.
- **Solvent Mass Fraction** Water/Acetonitrile System **Solubility Curve for Form I** (B) 0.25 **≟** 0.20 증 0.15 -0.05
 - 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 antisolvent crystallisation in this system is ~40% lower than a cooling crystallisation

Novel Miniature Platform Development for Morphology Optimisation

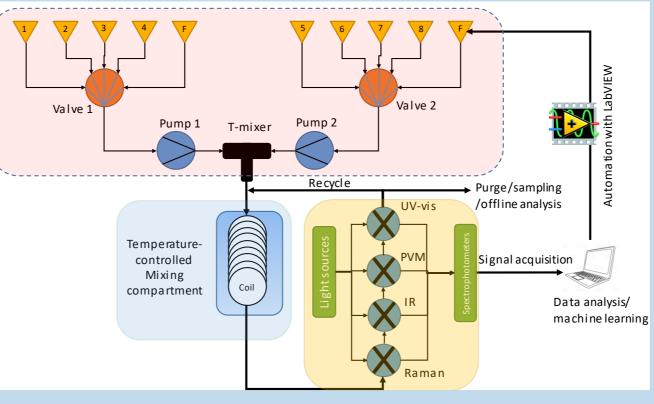
Feedback

control

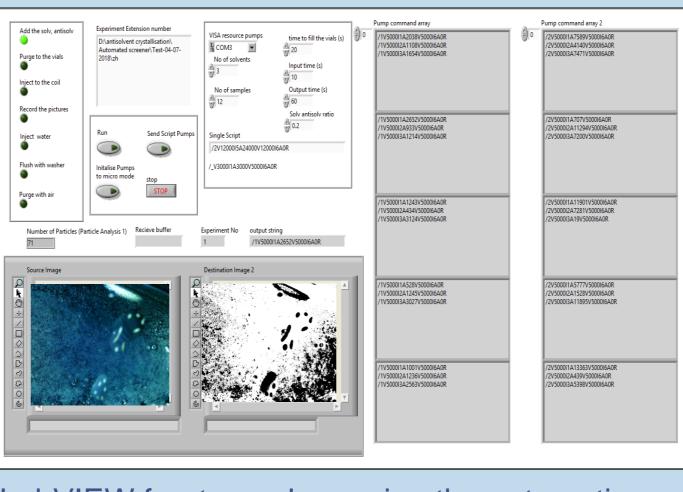
Automation &

visualization

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.

6-valves Syringe pumps

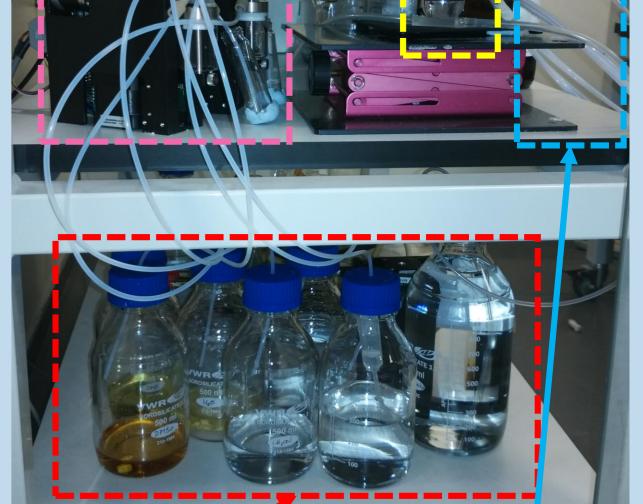
Cross mixer

microscope

USB

of Lamivudine

Quartz Flow cell



3 Solvents and 3 Antisolvents

Crystallization polytetrafluoroethylene coil

Conclusions

Solvent Mass Fraction

- 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.































