

# **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 Demonstration of crystallisation of modified stable Form I Lamivudine from batch continuous process? to a continuous platform • Improve the downstream process-ability by modifying Process the particle properties? translation • Develop miniaturise platforms for accelerated Modelling and feedback control/optimization of system process development? \*MSZW – Metastable zone width, \*AS - Antisolvent Lamivudine Morphology and Transformation **Early Stage Process Workflow** \***MSMP**R – Mixed-suspension, mixed-product removal \*COBC – Continuous oscillatory baffled crystalliser, Form II \*DoE – Design of experiment **Chemical structure** Experimental Anhydrous of Lamivudine Parameter estimation solubility •Automation **Bi-pyramidal** •System kinetics Induction Machine learning Thermodynamically times/\*MSZW favoured form Morphology Formed in anhydrous solvents Milled form II raw End platform **Miniaturised** Models Database material \*(MSMPR/COBC) platforms Form I 0.2 Hydrate Needle-like •Miscibility Marketed API (Epivir<sup>®</sup>) Rapid data collection Platform selection •Viscosity Unstable under •DoE Process optimisation ratios mechanical action Kinetics •AS nature Requires water activity AS workflow Recrystallised form I wet product of ~ 5 - 20% **Recrystallised** form



### **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



from cooling crystallisation

#### **Solvents Screening**

**Experimental Approach** Miniaturised parallel screening platform

# 15 vials with working volume

#### **DMF/Acetone System Solubility Curve for Form I**



Measured MSZ Limits Dilution Line Starting Points 0.35 0.30



0.10 -

maximum of 8 mL

## **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.

- 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-

# **Novel Miniature Platform Development**

### for Morphology Optimisation

**Feedback** 

control

visualization

from raw material

#### **Miniaturised autonomous** screening platform



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



### 6-valves Syringe pumps

USB microscope

**Cross mixer** 

**Quartz Flow** 

cell

brought to you by



**3 Solvents** and **3 Antisolvents** 



solvent crystallisation in this system is ~40% lower than a cooling crystallisation

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

Crystallization polytetrafluoroethylene coil

## 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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