

Background

Why the considerations for Lamivudine?

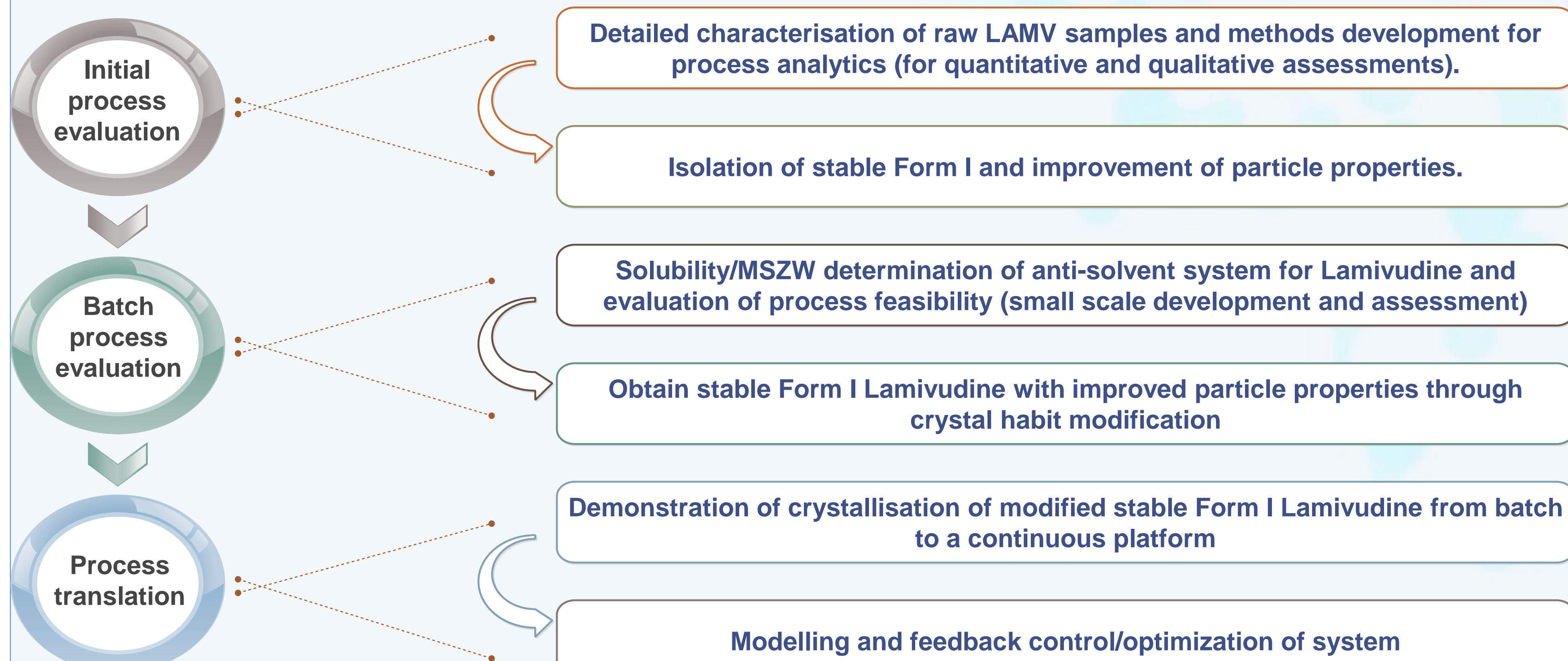
- Increasing numbers of HIV/AIDS infections on yearly basis (2.1 million new cases in 2015, UNAIDS)
- Hepatitis B infections (257 million cases globally, WHO)
- Currently FDA-approved antiretroviral therapy for the prevention and treatment of both viral infections (FDA).

Key research considerations and interests

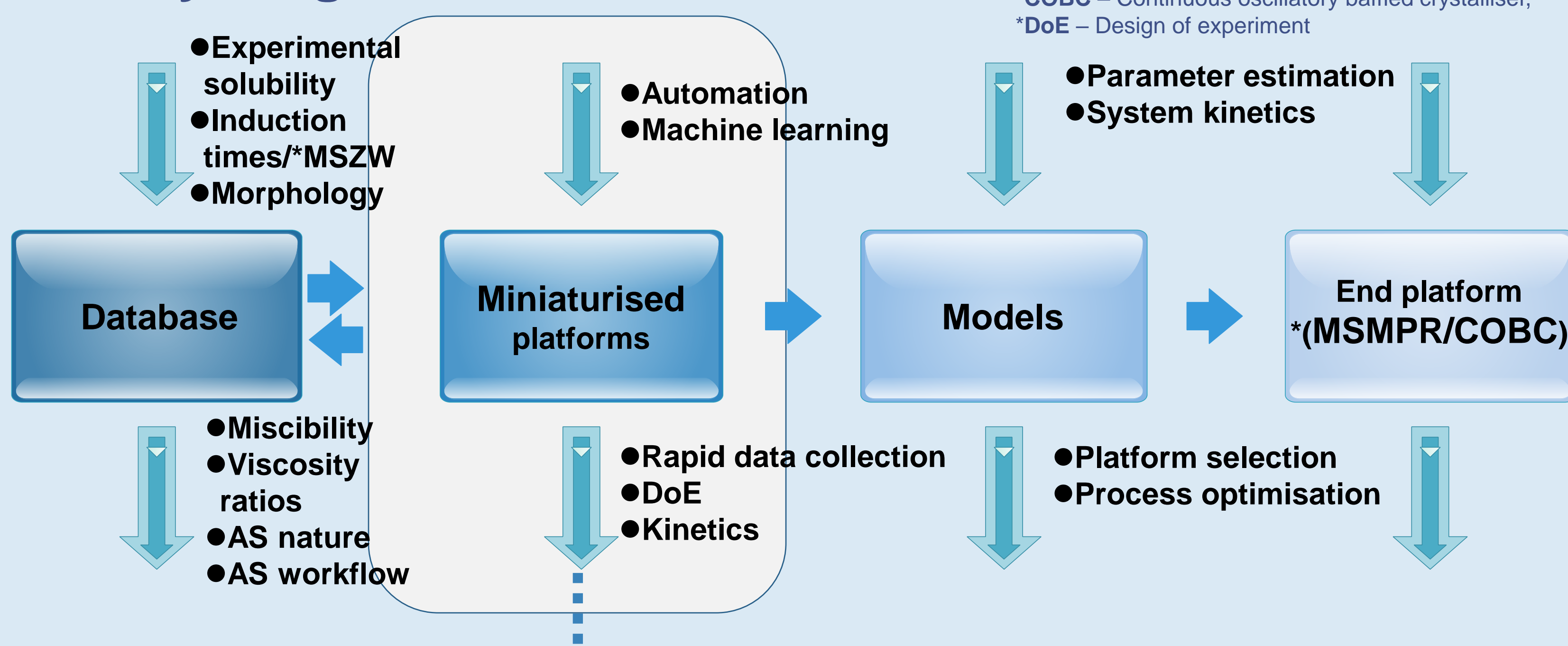
To the best of our knowledge, no publication yet exists on continuous manufacturing of stable Lamivudine form 1. The key research question here is:

- 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?

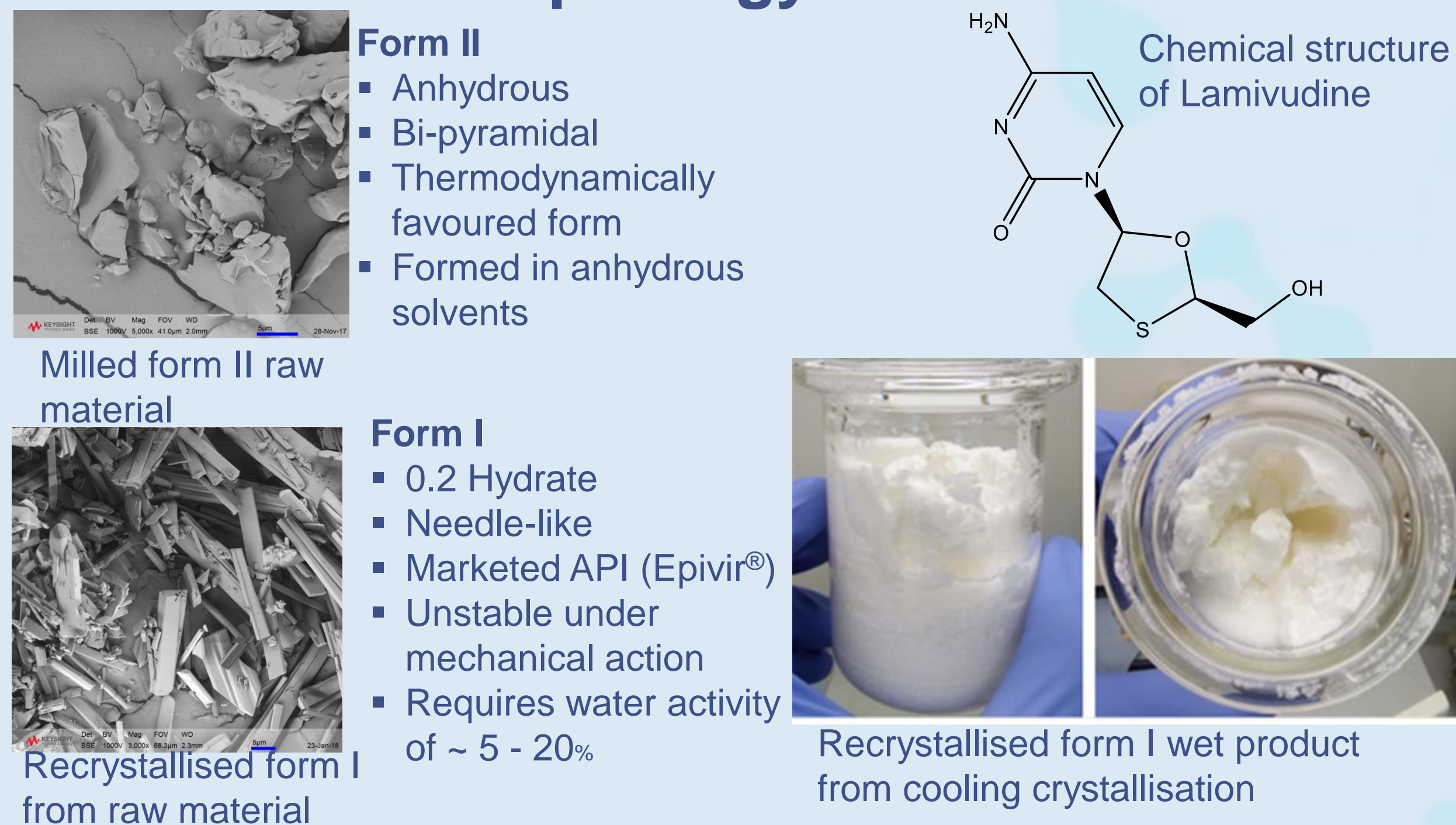
Objectives



Early Stage Process Workflow



Lamivudine Morphology and Transformation



Form II

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

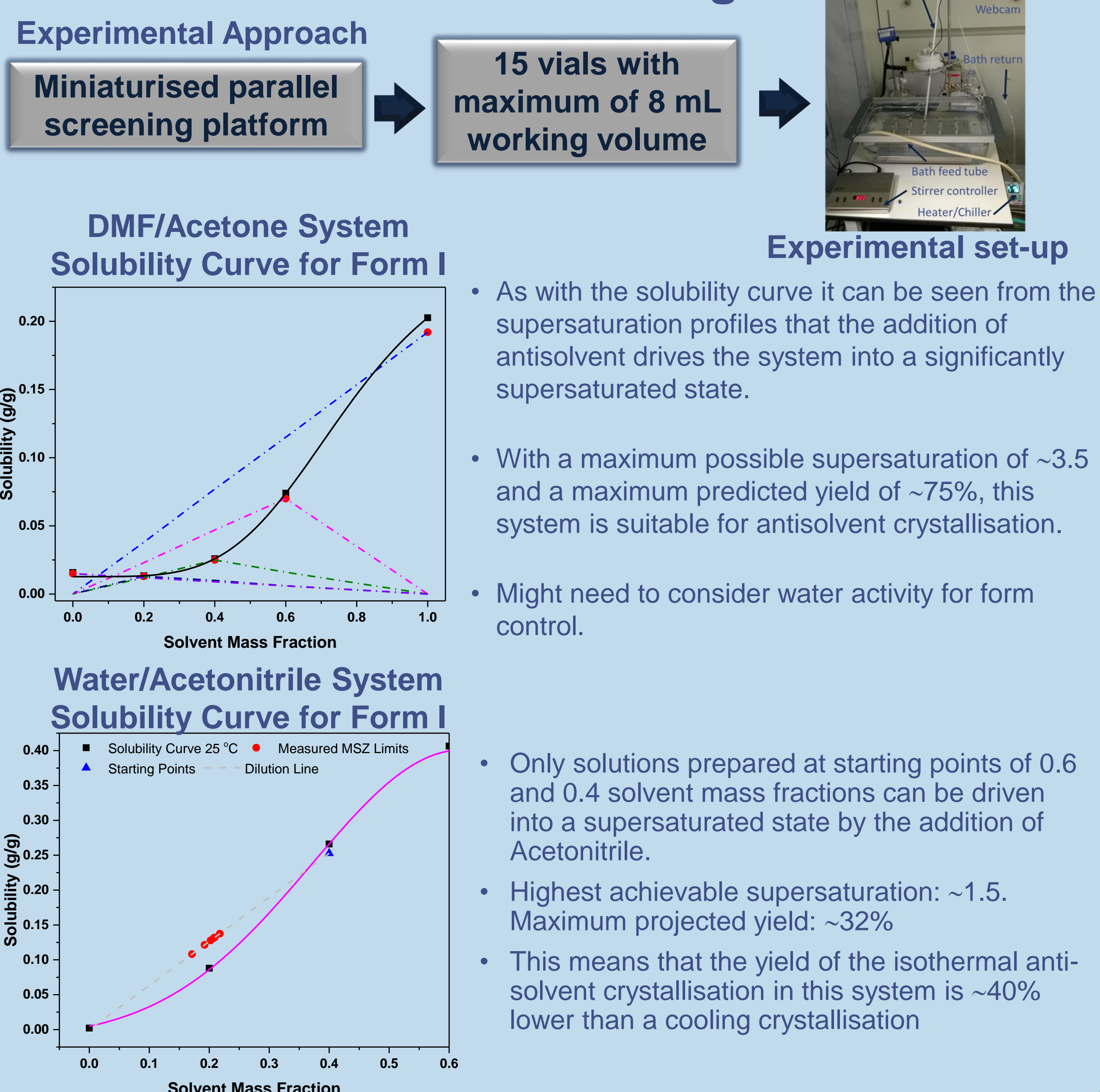
Form I

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

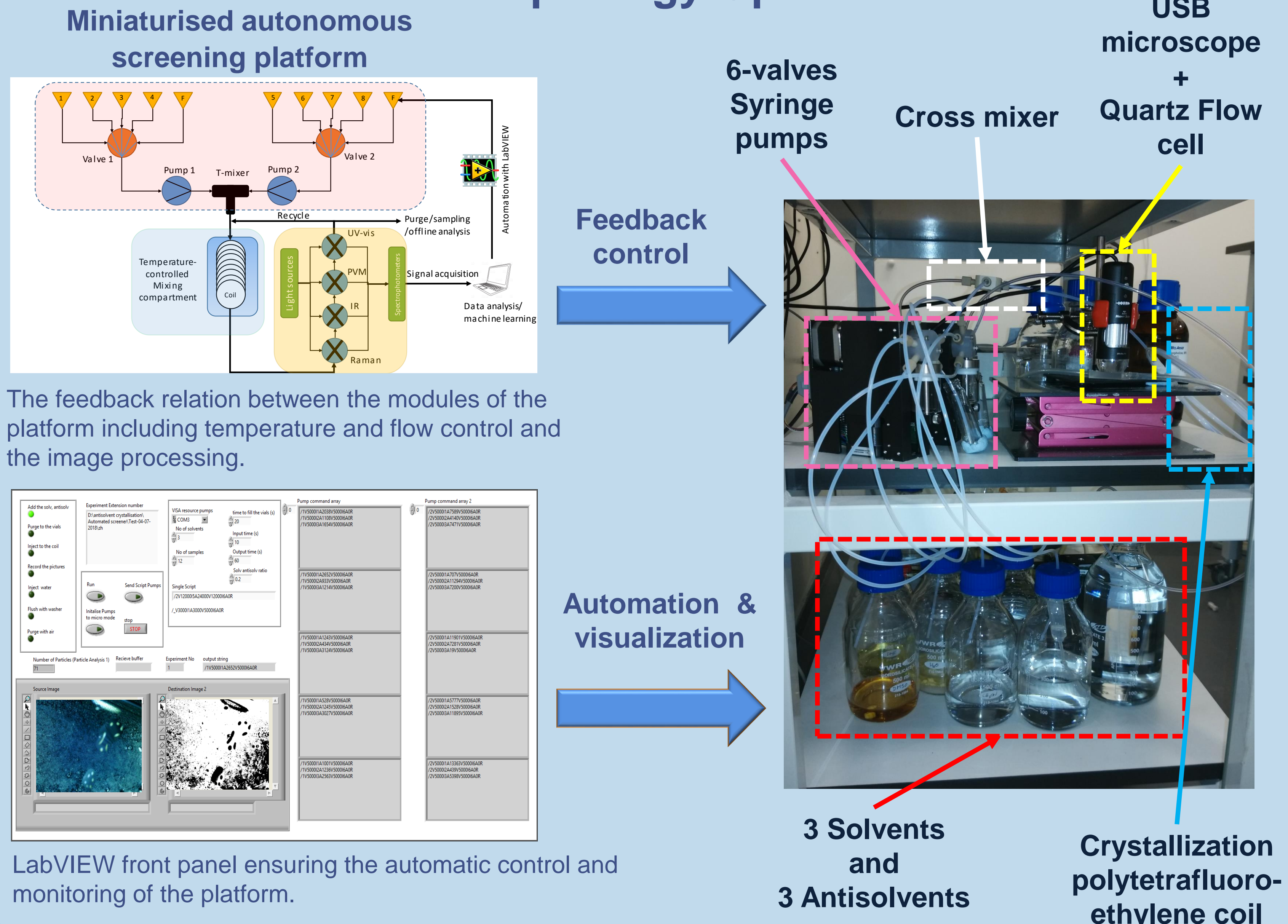
Chemical structure of Lamivudine

Images show: Milled form II raw material, Recrystallised form I from raw material, and Recrystallised form I wet product from cooling crystallisation.

Solvents Screening



Novel Miniature Platform Development for Morphology Optimisation



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

- Vasconcelos AT, Da Silva CC, Queiroz Júnior LHK, Santana MJ, Ferreira VS, Martins FT. Lamivudine as a nucleoside template to engineer DNA-like double-stranded helices in crystals. *Cryst Growth Des.* 2014;14(9):4691-4702. doi:10.1021/cg500786m
- Jozwiakowski MJ, Nguyen NAT, Sisco JM, Spancake CW. Solubility behavior of lamivudine crystal forms in recrystallization solvents. *J Pharm Sci.* 1996;85(2):193-199. doi:10.1021/js9501728

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.