POSTER 60

CMAC FUTURE MANUFACTURING RESEARCH HUB

A Structured Approach to Implementation of Measurements: Crystallisation in the Mefenamic Acid MicroFactory

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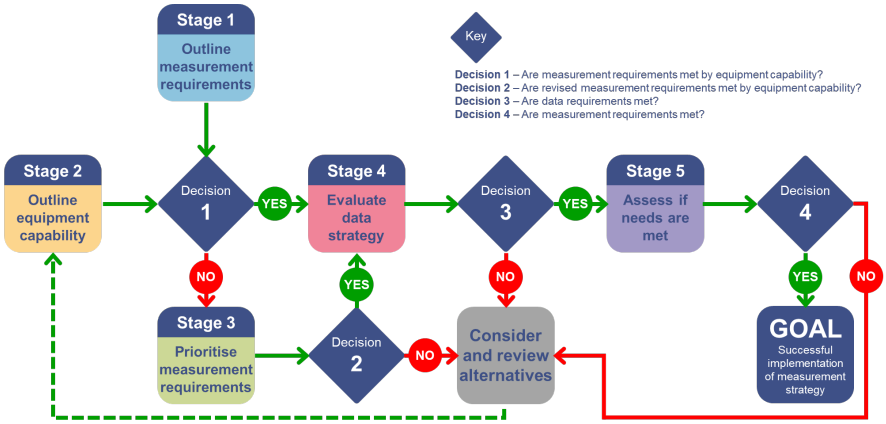


The CMAC workflow approach

Since the development of the seminal workflow for seeded continuous cooling crystallisations,[1] a number of workflows have been developed within CMAC that cover various processes including early stage crystallisation development,[2] impurity rejection,[3] and isolation.[4]

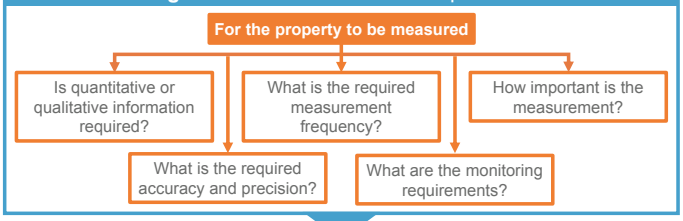
A workflow for implementation of measurements

The proposed workflow outlines stages and decisions normally undertaken in developing a measurement strategy. However, the suggested approach places measurement requirements at the forefront of all decision-making. The proposed structure therefore ensures all stages and subsequent decisions return to the measurement requirements outlined in Stage 1 of the workflow.

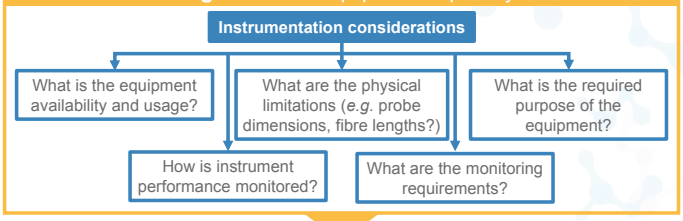
Case study: 5-stage crystallisation of mefenamic acid

The mefenamic acid MicroFactory includes a 5-stage crystallisation in 2-butanol/heptane (90:10 w/w). This crystallisation will be used to illustrate the decision making for *in situ* measurements according to the proposed workflow.

Stage 1 Outline measurement requirements



Stage 2 Outline equipment capability



Decision 1

Parameter to measure	Proposed *in situ* measurement
Mu0 (number of crystals)	Focussed beam reflectance measurement (FBRM)
D43 (volume mean size, crystals)	Particle vision measurement (PVM)
C (concentration)	Ultraviolet (UV) spectrometry

Are measurement requirements met by equipment capability?
✓ Single stage YES
× Multi-stage (equipment limitations) NO

Stage 3 Prioritise measurement requirements

Limitation: Unable to carry out measurements in all vessels.
- Use a sensitivity analysis approach to prioritise probe placements.

Physical constraints/challenges:
- Fitting of all probes into vessels.
- Positioning of instrumentation to maintain access to crystalliser.
- Ensuring equipment will not be disturbed (detrimental to data quality).

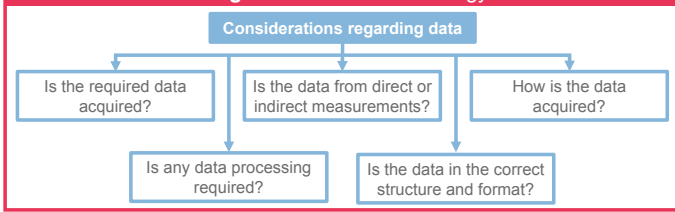
Additional constraint:
- Cannot accommodate Stage 5 proposal (subsequent equipment limitation).
- Compromise and revised probe placements required.

Sensitivity analysis approach	Stage 1	Stage 2	Stage 3	Stage 4	Stage 5
Model parameters for maximum size	FBRM UV	UV			FBRM
Process parameters for minimum size		FBRM UV	PVM		FBRM PVM UV
Process parameters for maximum size		UV	PVM	FBRM	FBRM PVM UV
Proposal	FBRM UV	FBRM UV	FBRM PVM		FBRM PVM UV
Revised proposal: considering physical constraints	FBRM UV	FBRM UV	FBRM PVM		FBRM PVM
Final proposal for probe placements	FBRM UV	FBRM UV	FBRM PVM		

Decision 2

Are revised measurement requirements met by equipment capability?
✓ YES

Stage 4 Evaluate data strategy



Stage 5 Assess if needs are met

Evaluation: Significant fouling observed in Stage 1.
- Relocate Stage 1 *in situ* monitoring to Stage 5 instead?

	Stage 1	Stage 2	Stage 3	Stage 4	Stage 5
Suggestion for future runs		FBRM UV	FBRM PVM		FBRM UV

Ongoing activities for improvements to future runs.

References 1. *Mol. Syst. Des. Eng.*, 2018, **3**, 518-549; 2. *CrystEngComm*, 2020, **22**, 7475-7489; 3. *Org. Process Res. Dev.*, 2020, **24**, 1443–1456; 4. *Org. Process Res. Dev.*, 2021, **25**, 1143-1159.

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