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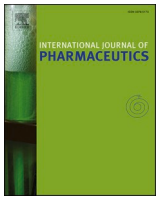

Quality by digital design in action: a workflow for crystallisation and isolation☆

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A B S T R A C T

This paper exemplifies a Quality by Digital Design (QbDD) workflow for the crystallisation and isolation of active pharmaceutical ingredients (APIs). QbDD uses a digital first approach to improve manufacturability and sustainability whilst assuring product quality within practical constraints. This study uses three exemplar compounds (ibuprofen, lamivudine, and AZD0837), each of which presents a different challenge for crystallisation; these include agglomeration, solid state form, and slow growth rates, respectively. These cases are used to evaluate the benefits of the QbDD approach and identify gaps for future research. Results of this work show that the QbDD workflow reduces the number of physical experiments by 28% and the API material usage by 52–65% when compared to comparable API development processes not using this approach. This approach provides a route to practically implement and exploit the benefits of digital tools and overcome digital skill shortages. By exploiting digital tools for process simulation and optimisation, the workflow improves efficiency, even in complex cases where multiple workflow iterations are required. This workflow, therefore, paves the way for more sustainable and cost-effective API production and it promotes future standardisation of digital design in pharmaceutical development.

1. Introduction

Pharmaceutical research and development (R&D) encompasses the steps to develop the processes and formulated products for an active pharmaceutical ingredient (API) and produce a medication that is safe and effective and of appropriate quality for patient use. To keep up with the ever-increasing speed of drug development (Conroy, 2023) innovation in product and process development must enable the pharmaceutical industry to deliver medicines to patients as fast, cheaply, and sustainably as possible (Schlander et al., 2021). This must be achieved whilst also exploring a large enough design space to reduce the possibility of in-development failures. Quality by design (QbD) is one of the

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approaches taken to assure the quality of medicines and enabling continual improvement to reduce costs and environmental impact.

In the 1990 s, QbD was proposed by Joseph M. Juran (Juran, 1992) and adopted by the U.S. Food and Drug Administration (FDA) for pharmaceutical use (Caphart et al., 2006). QbD builds on quality by testing (QbT) and quality by control (QbC) (International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use, 2008; Juran, 1992). QbD involves identification of a quality target product profile (QTPP) to allow selection of the critical quality attributes (CQAs). Performing risk assessments enables the identification of critical material attributes (CMAs) and critical process parameters (CPPs) and understand their relationship to each other, allowing development of a suitable control strategy (International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use, 2010a). By integrating QbD, manufacturers can develop robust, science-driven processes that consistently produce high-quality pharmaceutical compounds, accounting for the influence of material attributes, process parameters and related risk factors (Azad et al., 2021; Barshikar, 2019; Davis and Schlindwein, 2018; Yu et al., 2019).

With the introduction of Industry 4.0 and 5.0 (Arden et al., 2021; Azizi and Barenji, 2023; European Commission, 2022; Gong et al., 2025; Popov et al., 2022) and the associated innovations in digital technology and automation, digitalisation of chemistry manufacturing and control (CMC) development is both feasible and desirable. Quality by Digital Design (QbDD) builds upon the principles of QbD (Yu et al., 2019), integrating digital technologies, data analytics, and modelling tools into the drug development and manufacturing process (Mustoe et al., 2025 and references therein). In this work, the authors exemplify a QbDD workflow for CMC process development. This digital-first approach allows for a digitally augmented exploration of the process design knowledge space to enable the production of APIs with the desired attributes while reducing development time and costs. This digitally augmented design space should reduce the risk of product development failure and improve product and process resilience. QbDD enables efficient product quality assurance whilst optimising against sustainability and business targets within practical constraints. For the benefits of QbDD to be realised, fully linked systems-level models are required with integration of cyberphysical systems and data architectures.

Workflows for process development have also been reported in other studies (Agrawal et al., 2023; Brown et al., 2018; Cote et al., 2020; Gioiello et al., 2020), and implementation of mechanistic, data-driven, and hybrid modelling has been demonstrated (Nagy, 2008; Pankajakshan et al., 2025; Sansana et al., 2021). These studies have shown the benefits of using predictive models and implementing cyberphysical systems such as self-driving laboratories to investigate individual processes, subprocesses and process options (Aspuru-Guzik Group, 2024; Hein, 2021; Meng and Liu, 2023; Pickles et al., 2024b).

In this article, we describe the workflow proposed by Mustoe et al. and implement for crystallisation, isolation and drying processes for three pharmaceutical compounds: 1) ibuprofen, which is widely studied in the crystallisation literature (Dwivedi et al., 1992; Jolliffe and Gerogiorgis, 2015; Lukman et al., 2015; Mustoe et al., 2025; Nguyen, 2013; Ostrowska et al., 2015); 2) lamivudine, a comparatively lesser-known compound with a handful of crystallisation studies (Du et al., 2015; Harris et al., 1997; Jozwiakowski et al., 1996; Pickles et al., 2024a) and 3) a recent developmental compound produced by AstraZeneca, AZD0837 (Deshmukh et al., 2020; Yang et al., 2024) for which no prior knowledge for the crystallisation and isolation has been reported. Each of these compounds presents a different challenge for the crystallisation and isolation processes. The aim of this paper is to evaluate and quantify the benefits of a QbDD workflow for crystallisation and isolation of 3 APIs using available digital tools, ensuring product quality whilst optimising against industrially relevant manufacturability and sustainability metrics within practical operating constraints.

2. QbDD workflow for API crystallisation and isolation development

The purpose of the QbDD workflow is to use predictive models to explore a digitally augmented design space alongside materials-sparing experimentation. The QbDD workflow employs model-driven product and process understanding to enable identification of CMAs, CPPs, and CQAs. In this paper, the workflow is demonstrated for the crystallisation and isolation of APIs, but the QbDD approach is applicable across the whole of CMC development and is actively under development.

The QbDD workflow and associated methods are a culmination of academic and industrial collaborations as part of the Future Continuous Manufacturing and Advanced Crystallisation Research Hub (UKRI et al., 2025) and results from continual improvement throughout these three case studies. While this workflow guides users through the digitally enhanced process development, expert user input (human in the loop) will also be required to make informed, recorded decisions that may deviate from the schematic presented. The workflow is presented in linear form for simplicity but users may return to earlier stages to re-iterate workflow stages as new data are generated and/or predictive models improve. Stages 11 and 12 are out of scope for this paper but shown here for completeness. Each of the QbDD workflow stages, and a summary of the outputs is given in Table 1. Stages 1–4 are *in silico* conceptual design, Stages 5, 6 and 10 are integrated experimental and digital and Stages 7, 8 and 9 address risk and control evaluation plus

Table 1
QbDD workflow.

Workflow Stage	Outputs
1. Collate & Calculate API Prior Knowledge	Collation of known data and data that can be predicted.
2. Set QTPP, Sustainability & Manufacturing Objectives	QTPP and systems-level objectives set to absolutely assure quality whilst optimising against manufacturability and sustainability targets.
3. Select Conceptual Process Options	List of possible process options identified and ranked with the preferred process option selected for further investigation.
4. Identify Modelling Approach	Available model option(s) identified and ranked for each unit operation and equipment option(s) identified for that unit operation
5. Model Calibration & Refinement	Models parameterised for each unit operation using scale-down experiments. Process options then evaluated using model predictions vs process objectives. Process options then ranked, and preferred options identified.
6. Model Driven Design Development & Validation	Model parameters refined, process models validated, non-modelled phenomena that could affect the process investigated, and process operating constraints identified.
7. Initial Quality Risk Assessment	Quality risk assessment done for highest priority process option(s) with provisional CMAs and CPPs identified.
8. Identify CQA, CMA CPP & Design Space for Process	Practically operable design space optimised against process objectives, and CPPs that must be controlled to deliver required CMAs identified.
9. Model Driven Control Strategy & Risk Assessment	A control strategy is defined that ensures equipment, process monitoring and analyses are able to operate within the operating space and deliver material of required quality.
10. Operate Process & Assess Model Credibility	Material produced and tested to determine if material meets relevant CQAs and/or CMAs. Process and model performance evaluated.
11. Product Performance Analysis	Final drug product material analysed to determine if material meets QTPPs and model performance evaluated (not covered in this paper).
12. Product Lifecycle Management/Continuous Improvement	QbDD principles for product lifecycle management and continuous improvement established (not covered in this paper).

digital optimisation.

2.1. Stage 1 – Collate & Calculate API prior knowledge

Stage 1 collates existing knowledge and queries predictive tools to provide base data for development including, but not limited to:

- The classification of the API, based upon the biopharmaceutical classification system (BCS), developability classification system (DCS) and manufacturability classification system (MCS) (Abuhassan et al., 2024, 2022; Amidon et al., 1995; Butler and Dressman, 2010; Prasad et al., 2022; Silva et al., 2023) and enhancements to these systems being developed at CMAC (crystallisation classification system (CCS), manufacturability classification system plus (MCS +) and bioperformance classification system (BPCS) (CMAC, 2022a, b)
- Structural information (information from Cambridge Structural Database (CSD), e.g., morphology, polymorph landscape, co-crystals, co-formers) (Groom et al., 2016)
  - Physicochemical data for the API and existing formulations including solubility prediction
  - Manufacturing routes, companies and sites (if any)
  - Review of scientific and patent literature

2.2. Stage 2 – Set QTPP, sustainability & Manufacturing objectives

This stage sets the objectives and product performance requirements for process development and manufacture. First, all quality characteristics in the QTPP must be achieved to assure desired quality and, thus, efficacy and patient safety. Next, desirable criteria for manufacturability and sustainability are identified. Typically, manufacturability and sustainability targets are generic based on downstream process and business requirements. Finally, operational considerations and constraints such as health and safety considerations as well as practical operational constraints must be considered (Table 2), such as solids loading for slurry transfer, supersaturation levels, or maximum feed rates.

Each organisation should build relevant templates and checklists for these categories in line with QbD guidelines and local regulations. The checklist should be reviewed regularly and updated throughout the workflow as new information is gathered. This live document should be used to make transparent, traceable, science-based decisions but should be version controlled and archived at regular intervals.

Table 2
Determining objectives in Stage 2.

Objective	Description	Priority
Quality	QTPP: A prospective summary of the quality characteristics of a drug product that will be achieved to ensure the required quality, taking into account safety and efficacy of the drug product (International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use, 2010a).	Required
Manufacturability (usually for drug product)	Desired material attributes to improve ease and efficiency of downstream manufacturing.	Highly Desirable
Sustainability	Process targets that reduce environmental impact including reductions in energy use, resources and carbon footprint and the use of greener solvents and materials. Often set at organisational level.	Highly Desirable
Operability	Constraints that the process must operate within to meet health and safety requirements as well as operational process constraints. These constraints will be used to bound the model design space and sensitivity analysis to deliver realistic, operable optimal process conditions whilst ensuring patient safety.	Constraints

References:
1 ICH Pharmaceutical development Q8(R2), Aug 2009
2 Pharm Dev Technol, 2015, 20(1): 12–21

2.3. Stage 3 – Select conceptual process options

Using the information available/obtained in Stages 1 and 2, the specific process configuration options are selected considering available equipment (i.e., feed, seed, mill, mixed-suspension, mixed-product-removal (MSMPR) crystalliser, Nutsche or semi-continuous filters, drying, feed, blend, compaction, hot melt extruder (HME)/print etc.). Possible process options are identified and desirability ranked based on the availability of equipment, existence of a corresponding model and/or digital twin and researcher experience with both the equipment and the models. Preferred process option(s) are selected for further investigation. Ideally a single option is progressed, but multiple options can be carried forward where an obvious lead option is not identified.

2.4. Stage 4 – identify modelling approach

Relevant models for simulating the conceptual unit operations and equipment options available are identified, either from the organisation's model library or publicly available sources. The context of use for each model is determined based on Stages 1–3 of this workflow. The risks associated with model options are assessed, and models are evaluated for their ability to meet the required context of use. If multiple suitable models exist, then the optimal model(s) are chosen, and justifications for decisions are recorded with considerations including (but not limited to) model maturity and related data quality or potential bias. If no suitable models are identified, then, either new models can be developed where time and expertise allows or traditional experimental-based process development can be carried out.

2.5. Stage 5 – Model calibration & Refinement

The models' data requirements are identified, prior knowledge from Stages 1–4 is reviewed and, if initial model parameters are not available from prior data or predictions, targeted experiments are identified. The targeted, small-scale, materials-sparing experiments carried out in this stage should include the evaluation of solvents, reagents, and excipients, and the experiments needed to verify literature and predicted data. The models are parameterised with this data, and the *in silico* results of modelled process options are evaluated against Stage 2 process objectives. Uncertainties in data measurement should be incorporated throughout the model. Additional experiments may be caried out if increased certainty is required. If the objectives have been met, then a risk assessment is carried out for suitable process option(s), process options are ranked and justifications for decisions are recorded.

2.6. Stage 6 – model driven design development & validation

For each process option brought forward from Stage 5, a flowsheet is generated. The unit operations and available equipment are examined to identify the likely modelled and non-modelled phenomena within that process option. As physical rate processes can change with both scale and equipment, modelled phenomena are assessed by designing larger scale, more detailed experiments using process-representative equipment to re-parameterise the models with reduced uncertainty. If model uncertainties are still too high to assess model results against Stage 2 process objectives, further experimentation, equipment or analysis may be needed.

The non-modelled phenomena are assessed by targeted experiments. These experiments evaluate the impact of non-modelled phenomena on quality and operability, resulting in an understanding of the practical constraints for the viable process operating window. Constraints are recorded in the Stage 2 Process Objectives document and are

incorporated into models where relevant.

Both the model and the impact of the non-modelled phenomena are assessed against the results of validation experiments. If experimental results meet the model validation criteria, the researchers continue to the next stage. If not, the cause of the discrepancy is identified, and the researchers return to an earlier stage of the workflow to address it. It should be noted that these validation experiments may or may not be run in the identical to the equipment used in Stage 10, proof of concept run and thus, further validation may be required if equipment or scale changes.

2.7. Stage 7 – Initial quality risk assessment

The preferred process and equipment option is confirmed (this may occasionally be 2 or 3 options if there is no clear preferred option). A systems-level risk assessment is carried out for quality requirements as described in the QTPP in line with ICH Q7, Q9, Q11, and Q13 guidelines. The models are also used to help identify likely areas of risk and possible risk mitigation strategies for further investigation in Stage 8.

2.8. Stage 8 – Identify CQA, CMA, CPP & design space for process

The process objectives originally drafted in Stage 2 are reviewed, and target values agreed. A GSA is carried out that includes the practical constraints identified during the evaluation of the non-modelled phenomena in stage 6.

If a practical operating process envelope can be found within the overall design space that meets the quality requirements, then the optimal operating area is identified using multi-objective optimisation against manufacturability and sustainability metrics and carried through to Stage 9. If no suitable design space can be found, a sensitivity analysis is carried out to identify which model inputs have the greatest impact on the process outcomes. The inputs with the highest impact are evaluated to determine whether the desired process metrics or constraints can be relaxed to enable the process to meet the revised targets (n.b., quality related values are never relaxed).

Once the optimal design space is identified, the process model(s) are reviewed to identify where CMAs are formed and where the CMAs can be affected by the upstream process operations. This information is used to identify the CPPs that must be controlled to assure the product quality requirements are met as per ICH guidelines.

2.9. Stage 9 – Model driven control strategy & risk assessment

The control objectives are identified, initially at a systems-level, and then at unit operation/equipment item level. Process dynamics modelling and disturbance analysis is used to develop a control strategy. Where models do not exist or are not of sufficient fidelity, additional experimentation may be required to confirm equipment or analytical control and measurement capabilities, especially if operating close to the identified CPPs bounds (ICH Q8 and Q11) (International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use, 2010a, 2010b).

2.10. Stage 10 – Operate process & assess model credibility

The equipment is assembled into its final operating configuration and is commissioned. All relevant documentation (e.g. process instruction sheets, safety evaluation, risk assessments, operator training etc.) are completed. The process is then operated at the desired scale under the process conditions identified by the models. Models are used to help define the start-up and shutdown procedures, minimum run times to achieve a state of control where applicable and predicting run times for producing sufficient material for future processing, necessary sampling and testing.

This step identifies if the material produced meets all specifications applicable to its current form, i.e., the QTPP, manufacturability and sustainability criteria, by carrying out any required testing. Results are used to evaluate whether the model-based design successfully met the required objectives set in stage 2. If the product does not meet specification and/or the model does not meet the credibility criteria, then a root cause analysis should be carried out and the team return to the appropriate workflow stage identified to address it.

3. Exemplification of QbDD workflow for crystallisation and isolation

Three case studies are outlined in which the QbDD workflow was used for crystallisation and isolation process development of oral solid dosage forms. As the QbDD workflow was in development over the course of these case studies, not all stages were completed for each API (ibuprofen, lamivudine, and AZD0837). The research teams followed the same general approach typically involving API solubility prediction, crystallisation population balance modelling, computational fluid dynamics for changing equipment set-up or scale and a range of isolation models, but were free to select the optimal models and approach. Full models used, data and rationale for decisions made can be found in section 3 of the ESI.

3.1. Design intent and objectives for case studies

The following were adopted as common process design principles for all 3 compounds: a) process targets and objectives must be industrially relevant; b) tablet formation by direct compression; c) crystallisation by continuous processing and restricted to commonly available industrial equipment; and d) crystallisations would be seeded to optimise particle size distribution (PSD) control to improve flowability (Liu et al., 2008). The general process objectives used in Stage 2 of the workflow for each compound were aligned with the MCS guidelines to produce particles with the required attributes for direct compression and industrially relevant sustainability metrics (Table 3).

The equipment available in the laboratories at the appropriate scale includes MSMPR platforms (variable number of stages (1–5) and volume between 250 mL and 2 L), or batch equivalents with options for a wet mill for size control or nucleation, an AWL CFD25 unit for filtration, and subsequent tray drying. Unless otherwise specified the standard vessel setup was as per the MSMPR reported by Urwin *et al.* (Urwin et al., 2023).

The standard modelling approach taken uses mixed crystalliser population balance within gPROMS FormulatedProducts 2023.1.0 (Siemens, 2025a, 2025b) for the crystallisation (which also had the possibility of adding a wet mill) and isolation models developed by Ottoboni *et al.* (Ottoboni et al., 2021, 2022).

Table 3
Generic Manufacturability and Sustainability Targets.

Manufacturability Targets	Good	Acceptable	Method
Flow Function Coefficient (FFC)	>10	4—10	Schultz Shear Cell
Particle Size (μm)	$100 < D_{50} < 200$	$50 < D_{50} < 300$	Morphologi G3/M4

Sustainability Targets		Aspirational	Good	Acceptable
Dry Isolated Yield		> 97 %	> 90 %	> 80 %
Solid Mass Fraction at end of Crystallisation		> 20 %	> 12 %	> 6 %
Product Mass Intensity (PMI) at steady state	Crystallisation	< 5	5–8.5	8.5–16
	Isolation	1.2 – 1.5	1.5 – 2.0	2.0 – 3.0
	Whole Process	< 6.5	6.5 – 10.5	10.5 – 19
Number of Unit Operations		< 3	3	3 – 5

3.2. Ibuprofen

3.2.1. Ibuprofen: Stages 1–5

Stage 1: Ibuprofen is well characterised and reported in the crystallisation space (Dwivedi et al., 1992; Jolliffe and Gerogiorgis, 2015; Lukman et al., 2015; Nguyen, 2013; Ostrowska et al., 2015). The literature was not used for Stages 1–5 to evaluate the workflow but was utilised from Stage 5 onwards.

A solvate propensity model based on the methodology reported by Xin *et al.* (Xin et al., 2019) was used to assess the probability of ibuprofen forming a solvate (unpublished work). The results indicated that ibuprofen is unlikely to form solvates with any of the solvents present in the common solvates in the Cambridge Crystal Structure Database since all probabilities are below 0.5. COSMO*therm* screening with no reference data was carried out to rank the common solvents at 25 °C (this work is reported in stage 5 to simplify the narrative for the reader).

Stage 2: The essential quality metrics for the ibuprofen crystallisation process are chemical purity (98.5–101.0 %), solid state form (Form I), particle size, and residual solvent levels (<0.5 %) following standard ICH guidelines. To estimate the particle size requirements to achieve complete oral absorption, a refined Developability Classification System (DCS) approach (Rosenberger et al., 2018), implemented in BASF ZoomLabTM was used (BASF Pharma, 2022). For ibuprofen, values supplied within ZoomLabTM for Ibuprofen 50 (purchased from BASF) for the solubility in fasted state simulated intestinal fluid (FaSSIF) at 37 °C and effective intestinal permeability were used as 2.10 mg/mL and 2.13x10-4 cm/s, respectively. These values result in a dose number (Do) and absorption number (An) of 0.19 and 2.2, respectively thus placing ibuprofen as a DCS class I (high solubility, high permeability), with a maximum D90 for complete dissolution during intestinal transit of 490 μm.

Stages 3 and 4: A single crystallisation followed by isolation using filter, wash, deliquor, and drying (both contact and convective) was identified as the preferred processing route based on the fewest unit operations (ESI 3). Standard models were available for these options.

Stage 5: Crystallisation: Screening of single solvents was carried out using a combination of COSMO*therm* and experimental verification. Most solvents screened exhibited high solubility except heptane. The yields were still relatively low unless operationally difficult low final temperatures were considered. Thus, binary solvent systems were screened focusing initially on heptane/alcohols and then water/alcohols or water/acetone using g-SAFT as ibuprofen had been previously parameterised and, in our experience, typically gives more accurate solubility predictions (Watson et al., 2021). Extension of the work of Watson et al. identified ethanol/water as the optimal solvent system with the highest yield, although heptane/2-pentanol and water/acetone were also taken forward as the yield differences were less than 10 %.

Small-scale polythermal screening experiments were carried out in the Crystalline (Technobis) to verify the solubility predictions and identify any possible risks (e.g. adverse habit, floating or sinking particles, agglomeration, adherence of crystals to walls or agitators). Oiling out was observed in water/acetone systems so this was discarded as a process option (see ESI section 3.2.1, stage 5). Agglomeration was observed in the ethanol/water systems, especially above 60 % water. A multidisciplinary team reviewed the results and identified ethanol/water as the solvent mixture that best meets all the objectives identified in QbDD stage 2 with a risk of agglomeration identified. Furthermore, an isothermal antisolvent crystallisation can satisfy all the criteria without the need of a cooling step (avoiding additional risk of hot solution transfers).

Stage 5: Isolation: In parallel to the solvent selection work, candidate wash solvents were initially evaluated using COSMOtherm with water, heptane, and cyclohexane being preferred due to low solubility at room temperature, ease of drying, and cost. Cyclohexane was excluded due to its higher cost compared to heptane, despite having similar properties. The candidate wash solvents were tested using a Biotage system consisting of filtration tubes and a vacuum filtration station ISOLUTE® single fritted reservoir 70 mL 20 μm PE, VacMaster Sample Processing Station, Biotage GB) for different crystallisation water/ethanol compositions. Water caused unwanted precipitation and agglomeration, whilst neither phase separation nor dissolution were observed with heptane. Thus, heptane was selected as the wash solvent. Once the crystallisation solvent composition was fixed, a 44 mL suspension (10 % solids in saturated 60/40 water/ethanol mixture) was filtered and washed with 13.7 g heptane (2 × cake volume) to give a 1.03×10^{-5} m^3 cake with low resistance (1.21×10^8 m/kg).

3.2.2. Ibuprofen Stage 6

Literature data for growth and secondary nucleation kinetics (Rashid et al., 2017, 2012, 2011) were used to parameterise a population balance model in gPROMS FormulatedProducts 2022.1 and the global optimiser was performed for several scenarios. The water content was set to 50 % and 60 % (based on COSMO results to maximise yield whilst minimising agglomeration) and a 3 or 5 stage MSMPR system (standard laboratory setup) was evaluated against QbDD Stage 2 (Section 2.2). The highest yields (88–91 %) were obtained with 60 % water content and a particle size D_{50} of 100 μm and D_{90} of around 200 μm was predicted in all cases. A 3-stage MSMPR system with a crystallisation solvent of ethanol/water (maximum 60 % water) and heptane as the wash solvent was selected as the preferred process for onward evaluation.

Non-modelled phenomena evaluation: The solubility was found to be slightly higher than the literature values (Rashid et al., 2009) and a revised solubility curve was obtained and used for all further modelling. A slurry transfer test was carried out and a slurry with 20 % solids loading was successfully transferred between two vessels without any size segregation of particles; this was deduced from *in situ* monitoring of the vessel contents using a focussed beam reflectance measurement (FBRM).

Ibuprofen with a specified D_{50} of 25 μm was purchased as seed material. The manufacturer's analytical method using a Malvern Mastersizer could not be replicated in-house due to equipment availability. Analysis of the seed using a Malvern Morphologi G3 gave a D_{50} of 76 μm with imaging indicating partial agglomeration of the material. It is not clear how much of the size discrepancy is from the different particle sizing techniques and how much is from the agglomeration. This also highlights the challenges in different particle sizing techniques often giving different results causing challenges for FAIR data and interoperability principles. To reflect real-life industrial challenges, this material was used to test the workflow.

The primary nucleation threshold (PNT) or metastable zone width was measured along with the growth and secondary kinetics using a sequential parameter estimation approach. Agglomeration was identified to be occurring during the growth evaluation experiments (also identified as a risk in Stage 5 work) so the agglomeration efficiency was modelled based on the Mumtaz number (Hounslow et al., 2001; Pérez-Calvo et al., 2016; Pitt et al., 2012) and parameterised from a seeded batch de-supersaturation experiment. The following kinetic parameters were obtained: primary nucleation rate constant (k_{b_1}) = 18.9 ln(#/m^3.s), surface energy correction factor (α) = 0.25, bridging strength parameter (A_{50}) = 0.0021 with standard deviations of 0.23, 0,023 and 6.2×10^{-4} respectively. Goodness of fit (i.e. model adequately fits the measured data) was assessed through a X^2 test to compare the weighted residual and the expected weighted residual. A good fit was achieved when X^2 was less than X^2-critical across all experiments and measurements used for parameter estimation (Table 4).

Sensitivity analysis was conducted to assess the impact of larger seed size on the process criteria. Multi-criteria optimisation in gPROMS FormulatedProducts 2022.1 predicted that the seed material with a D_{50} of 74 μm could not deliver the required PSD to meet the quality size target and desired manufacturability yield targets within the constraints of 10 % seed loading and > 80 % yield. Repeating the simulation using a seed size of D_{50} = 46 μm (size reduced using a high shear wet mill

Table 4
Comparison of predicted and actual results from ibuprofen validation run.

Material	Particle Size (μm, Morphologi G4)			Process Mass Intensity (Solid % in final slurry)	Isolated Yield (%)
	D_{10}	D_{50}	D_{90}		
Seed	20.3	37.5	79.7		
Slurry in vessel 3	76.54	159.2	295.2		
Isolated product	69.0	145.8	293.8	11.90 (13.1)	84.3
Model predicted	84.0	171.8	310.8	12.43 (12.8)	89
X^2			9.30		
X^2 – Critical			14.08		

Note: X^2 and X^2-critical values relate to the goodness of fit of the model at stage 6 used to design the validation run.

(HSWM)) (Urwin et al., 2023) still failed to meet the desired criteria. Evaluation of the QbDD Stage 2 criteria by the multidisciplinary team, coupled with global sensitivity analysis, identified manufacturability and operability targets that could be relaxed: yield and residence time. The optimal process conditions identified provided a yield of 83 %, residence time of 84 min, final water content of 58.8 %, final solids loading of 12 %, keeping supersaturation below 1.2 and, most critical for quality requirements, a D_{90} particle size less than 490μm. This model simulation significantly reduced the number of experiments and material required that would have been carried out compared to traditional trial and error approaches.

Verification runs: a 2-stage MSMPR process was carried out to evaluate the practical operation and model performance under process typical conditions. Significant blockages occurred in the transfer lines after ~ 2 h. Root cause analysis identified evaporation and slow slurry transfer as the most likely reasons, so the slurry transfer was changed from continuous positive nitrogen pressure to periodic positive nitrogen pressure transfer.

A full 3-stage MSMPR system was used in the next verification run. Improvements to the HSWM setup to avoid foaming resulted in a reduced seed size of D_{50} = 42 μm and the process conditions were re-optimised vs yield using the pre-existing model, resulting in higher yields and lower seed loading. Baffles were added to the vessels because bubble entrainment from the impeller vortex was adversely affecting the PAT measurements. Despite a blockage in the feed line terminating the experiment early, sufficient results were collected to identify reduced particle size and lower ibuprofen concentration in solution vs predicted values during the period before blockage. Root cause analysis identified the most likely cause as changes in the hydrodynamics due to addition of baffles and slower agitation speed resulting in higher shear and lower levels of agglomeration. Thus, the model was reparametrised with a revised bridging strength (A_{50}) of 0.0013.

3.2.3. *Ibuprofen Stages 7–10*

The only CQA during the crystallisation process is the final product D_{90} < 490 μm to meet oral bioavailability requirements. Fig. 1 identifies the CPPs and CMAs resulting from the D_{90} CQA with relevant rationale based on minimising agglomeration processes.

Sensitivity analysis was conducted using the updated model from Stage 6 with revised agglomeration kinetics, accounting for kinetic and operational variability reported in (see ESI section 3.2.3). The performance was assessed under nominal conditions, assuming 5 % total error. Uncertainties in growth, nucleation, and agglomeration kinetics were evaluated. The kinetic parameter effects identified were: agglomeration impacts critical particle size, growth affects API mass fraction and yield, while nucleation has minimal impact due to steady-state seeding. Investigation of the operational parameters showed that solvent ratio (EtOH/water) is most critical, followed by feed concentration and flow rate. The seed loading moderately affects particle size *via* its influence on surface energy, growth, and agglomeration. The operational parameters have a greater impact than kinetic parameters, emphasising the need for robust process control.

The only CQA at risk during the crystallisation and isolation is the D_{90} size limit (Fig. 1). The uncertainty analysis indicates that the predicted product D_{90} is almost 200 μm below the critical quality limit at a 95 % confidence limit and this provides a significant contingency. Detailed proven acceptable range experimental work was not carried out as the aims of the paper are to evaluate the workflow and not develop a fully current good manufacturing process (cGMP) process.

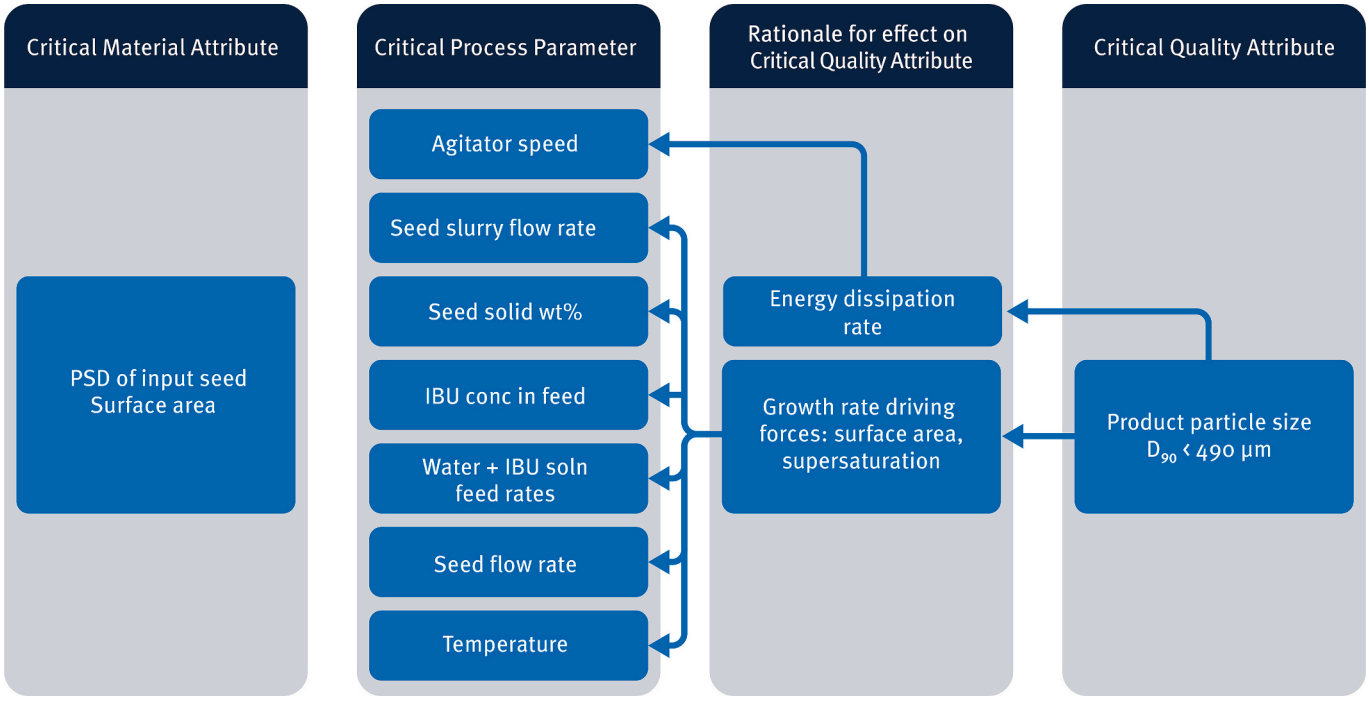

Fig. 1. Linking of CQA to CPPs and CMA for Ibuprofen.

Validation Run: The process was carried out using the optimal conditions identified from the gPROMs simulations using the revised parameters from the end of stage 6 (section 3.2.2) with periodic transfer of 10 % of the vessel volume (20 mL) of slurry transferred every 193 s. The system was operated successfully with no blockages for 346 min (4.2 residence times). The *in situ* particle size distribution measured using a Blaze probe is higher than that measured off-line using a Morphologi 4. This was attributed to the filtration and drying processing partially breaking some of the agglomerates.

Isolation was carried out using an AWL – CCFD (Alconbury Weston Ltd – Continuous Carousel Filter Dryer). A total of 13 isolation cycles were carried out, resulting in a total damp product mass of 65.425 g. After drying in a vacuum oven the resulting dried product had a D_{90} of 294 μm (CQA < 490 μm) and a final mass of 59.02 g which represents an 84.3 % final isolated yield (target/modelled value of 89 %). The final product PSDs are consistently lower than predicted and this is believed due to some attrition in the isolation stages which is not included in the model.

The quality criterion of the D_{90} PSD was satisfied (Table 4), and the manufacturability and sustainability metrics were achieved. The PMI values is higher than was ideal and further process development time would be expected to improve this as well as greater emphasis on optimisation vs PMI value.

3.3. Lamivudine

3.3.1. Lamivudine Stages 1–5

Stage 1: Lamivudine, a World Health Organisation essential medicine, is a nucleoside reverse transcriptase inhibitor used to treat human immunodeficiency virus (HIV) and hepatitis B (National Institute for Health and Care Excellence NICE, 2025). Lamivudine has three known solid-state forms (Forms I, II, and III), and X-ray powder diffraction (XRPD) data was collected in-house to obtain a reference standard (Du et al., 2015; Harris et al., 1997; Jozwiakowski et al., 1996) and was verified as the required Form II. While Lamivudine exhibits high solubility in water, its use as a primary crystallisation solvent is unfeasible due to formation of the undesired solid state Form I at water levels above 18 % (Jozwiakowski et al., 1996) and was not included in the initial single-solvent screening. COSMO*therm* screening was carried out to rank the common solvents at 25 °C and this work is reported in stage 5 for clarity of presentation.

The solvate propensity model (Section 3.2.1) was used to assess the probability of lamivudine forming a solvate in a selection of solvents. The results obtained show that lamivudine is unlikely to form solvates with any of the common solvates present in the Cambridge Crystal Structure Database since all probabilities are below 0.5.

Stage 2: The essential quality metrics for the lamivudine crystallisation process are chemical purity (98.5—–101.0 %), solid state form (Form II) and residual solvent levels (<0.5 %) in line with ICH guidelines. With bipyramidal geometry, Form II results in better flowability than the needle-shaped crystals of the Form I hydrate so Form II is targeted in this campaign. To estimate any particle size requirements to achieve complete oral absorption, a refined DCS approach, implemented in BASF ZoomLab^{TM} was used. For lamivudine, literature values for the solubility and intestinal permeability were used as 82.6 mg/mL (Steyn et al., 2016) and $0.33x10^{-4}$ cm/s (Patel and barve, 2012), respectively. This resulted in Do of 0.0073 and An of 0.34, placing Lamivudine as a class III (high solubility, low permeability) (Metry and Polli, 2022) drug. As oral bioavailability is limited by the intestinal permeability, there is no particle size target required from an oral absorption aspect and manufacturability considerations will determine the desired particle size.

Stages 3 and 4: The process chain was selected as crystallisation then isolation (filtration/washing/drying) to make material suitable for direct compression. The MSMPR platform was selected for initial evaluation for the crystallisation process. A Biotage filtration unit was selected for the isolation development work and the AWL CCFD25 Carousel for the main run (Ottoboni et al., 2022). Models exist for the equipment selected.

Stage 5 Crystallisation The solubility of lamivudine was predicted for single solvent systems using COSMO-RS using latent heat of fusion (20.84 kJ/mol) and melting point (178.6 °C) data (Chadha et al., 2012). Using the criteria of Pickles et al, a shortlist of acetonitrile, propan-1-ol, butan-2-ol, propan-2-ol, 2-methylpropan-1-ol and dimethyl carbonate were identified as suitable candidates. Verification experiments carried out in the Crystalline showed the COSMO-RS predictions to significantly over-estimate the solubility of Lamivudine. These data were used to revise the COSMO model. Methanol was the only solvent that met all the criteria, but was rejected due to toxicity concerns so binary solvent systems were investigated. Reviewing single solvent solubility data, ethanol/water and acetone water were further evaluated. As the solvent systems were potentially suitable for both antisolvent or cooling crystallisations, materials-sparing, experimental solubility curves and Metastable Zone Width (MSZW) were determined A mixture of Form II and Form I was isolated from samples taken from both solvent systems during this work so form I to Form II reslurry evaluation was carried out for both ethanol/water and acetone/water. A competitive slurry investigation (1:1 ratio of Forms I and II in a saturated solution) was conducted using a range of temperatures (5–20 °C) and water compositions (5–20 %). In all cases, the Form I converted to the desired Form II (measured by X-ray Powder Diffraction (XRPD) 9in between 30mins and 5 h with faster conversion rates observed at lower temperatures and lower water concentrations.

Following both the single and binary solvent screen, three possible solvent systems (Table 5) with five possible crystallisation modes were identified and theoretical mass balance was performed to compare processes based on PMI. Small scale validation experiments were performed to confirm Form purity in these scenarios. In acetone:water system risks of form purity were observed. The ethanol:water system met the stage 2 selection criteria of solid loading and isolated yield while maintaining Form purity (Table 5).

The successful conversion of form I to Form II during reslurry experiments data from seeded experiments, confirm that the risk of Form 1 formation can be mitigated by providing sufficient residence time during crystallization and was further mitigated by a seeding strategy to prevent primary nucleation of the hydrate.

Stage 5 Isolation: The solubility of lamivudine in n-heptane was predicted during the crystallisation solvent screen to be very low and was selected as the preferred wash solvent due to its low boiling point, similar density and viscosity to the mother liquor, and ICH class. The isolation selection procedure followed that outlined for ibuprofen (section 3.3).

3.3.2. Lamivudine Stages 6–10

Stage 6: Experimental statistical methods to measure the volume diffusion, surface integration, and attrition components of the

Table 5
Crystallisation solvent selection targeting polymorphic form, purity and manufacturability constraints.

Metric	**Ethanol**	**Ethanol:Water**		**Acetone:Water**	
Crystallisation mode	Seeded cooling	Seeded cooling (90:10) 60 °C	Antisolvent	Seeded cooling (90:10) 40 °C	Antisolvent
Solid loading wt%	5.5	10	20	5	18.8
Throughput g/g solvent	0.044	0.088	0.059	0.03	0.055
Isolated Yield %	80	88	85		88
Solid state	Form 2	Form 2	Form 2	Form 2	Mix Form 1 and 2

crystallisation model were carried out to parameterise a gPROMS Formulated Products (gFP) model for cooling crystallisation of lamivudine from 90:10 ethanol–water (wt/%). A growth-only model was most suitable for this system, with secondary nucleation having minimal influence.

In-silico optimisation of the continuous crystallisation process was conducted with the maximisation of yield defined as the objective function meeting the QbDD stage 2 target criteria within operability constraints. The optimum was predicted to afford above 90 % yield with a 159 min residence time for a 3-stage MSMPR process. No significant risks were identified from the parameterisation work so non-modelled phenomena were not practically evaluated further.

Stage 7, 8 and 9: The main risk item is formation of the undesired solid state Form I. Evaluation of the model showed no significant risk due to slow growth and no significant other rate processes (e.g., agglomeration or attrition) occurring.

The CQA affected by the crystallisation and isolation processes is ensuring solid state Form II. Fig. 2 outlines the CPPs and CMAs associated with the solid form.

The water level was maintained well below 18 %, seeding (optimised mass, surface area and seeding temperature) and sufficient process time for any Form I to convert to Form II (30 min to 3 h depending upon water wt%) was implemented to minimise the risk of hydrate formation. The final solvent levels were controlled by drying the material and testing.

Validation run: A seeded cooling crystallisation experiment of lamivudine in 0.9:0.1 ethanol/water in a 3-stage MSMPR cascade was carried out. The particle number and size in vessel 3 was monitored using FBRM and the solution concentration in vessel 2 was monitored by attenuated total reflectance mid infrared (ATR-MIR) spectrometry.

The continuous process was operated successfully for seven hours. One partial transfer line blockage occurred due to encrustation at the liquid surface while operating below the jacket line. This issue was resolved by increasing the vessel fill so the liquid surface was above the jacket line thereby reducing evaporation at the interface. Comparison of the experimental measured vessel concentrations and isolated product sizes with the model predicted values gave a good agreement (±0.05 % and 15 μm difference between actual and predicted values, respectively, Table 6) when accounting for growth rates and agglomeration parameters with better agreement between the experimental and modelled particle sizes. The X^2 – Critical value is higher than the X^2 value indicating a good fit for the model. The PMI value and yield were within experimental error of the predicted values. As for IBU, additional development or a longer residence time in a non-time constrained process operating environment and model optimization would reduce PMI to be more in-line with the process targets.

Table 6
Comparison of predicted and actual results from lamivudine validation run.

Material	Particle Size (μm, Morphologi 4)			Process Mass Intensity (Solid % in final slurry)	Isolated Yield (%)
	D_{10}	D_{50}	D_{90}		
Seed	7.99	26	71.3		
Slurry in vessel 3	130.1	270.6	488.3		
Isolated product	101.3	271.3	485.1	10.54 (10.5)	91.3
Model predicted	136.3	285.7	509.3	11.64 (9.1)	90
X^2	36.4				
X^2 – Critical	41.3				

Note: X^2 and X^2-critical values relate to the goodness of fit of the model at stage 6 used to design the validation run.

3.4. AZD0837

3.4.1. AZD0837 Stages 1–5

Stage 1: AZD0837 Fig. 3 was an API developed by AstraZeneca for use as a thrombin inhibitor (Fig. 33); a class of medicines used as anticoagulants which delay blood clotting (Deshmukh et al., 2020; Yang et al., 2024). The target dose was 150 mg and the molecule has a heat of fusion of 90 J/g and a melting point of 111 °C (DSC measurement). COSMO*therm* screening with no reference data was carried out to rank the common solvents at 25 °C (this work is reported in stage 5 to simplify the narrative for the reader).

The solvate propensity model (described in section 3.2.1) was used to assess the probability of AZD0837 forming a solvate in a selection of solvents. The results obtained predict that AZD0837 has a high probability to form solvates in all solvents screened. The unusually high results for AZD0837 could be attributed to an uneven representation of classes in this area of chemical space and as such the model results should be treated with caution and experimental evaluation carried out.

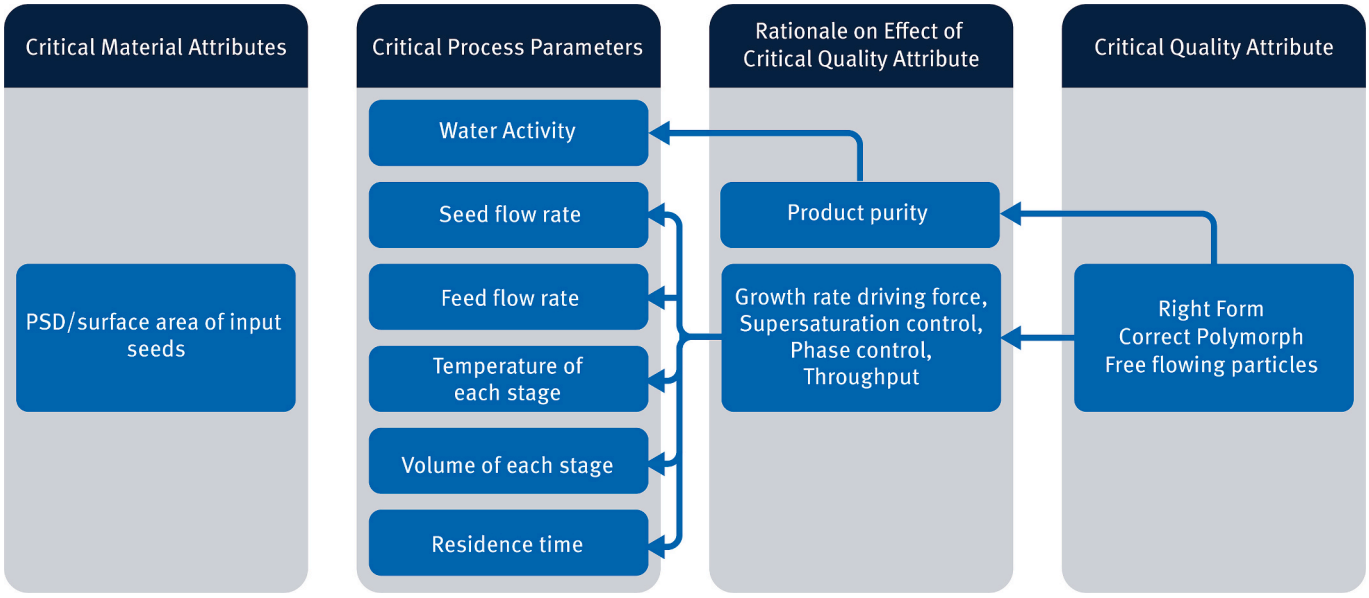

Fig. 2. Linking CQA with CMAs and CPPs for Lamivudine.

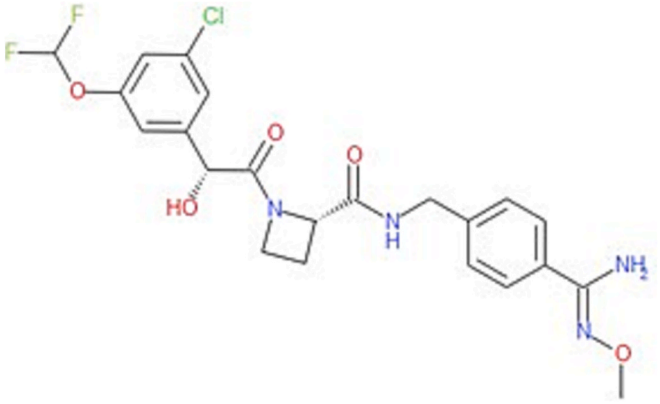

Fig. 3. Chemical Strcture of AZD0837.

Stage 2: The essential quality metrics for the AZD0837 crystallisation process are chemical purity (98–102 %), solid state form (maintain same form) and residual solvent levels (<0.5 %) based on ICH guidelines. While the compound is chiral, no chemistry is being carried out so the chirality of the product was not measured.

To estimate any particle size requirements to achieve complete oral absorption, a refined DCS approach, implemented in BASF ZoomLab™ was used. For AZD0837, the solubility was measured using a 9-point media system (Abuhassan et al., 2024) to range from 0.357 to 0.886 mg/mL. As no permeability data were available, a value predicted from molecular properties (Winiwarter et al., 1998) of $0.95x10^{-4}$ cm/s resulted in the Do of 1.7 to 0.68 and An of 0.95, placing AZD0837 predominately within class IV (low solubility, low permeability) but spanning across to class III. However, the An value also places it close to the boundary with class IIb (solubility limited). Based on this, the recommendation would be to formulate the drug product as an amorphous solid dispersion. As the intent is to carry out crystallisations as exemplars, a crystallisation approach has been taken here and, no particle size target is required from an oral absorption aspect at the crystallisation stage.

Stages 3 and 4: As with the other 2 compounds, the preferred process chain for the manufacture of AZD0837 would be crystallisation, followed by filtration/washing/drying, and the powder product using the MSMPR (or equivalent) and AWL CFD25 Filtration Carousel. Models exist for the approaches identified here.

Stage 5: Based on the solvent selection criteria (reported by (Pickles et al., 2024a)) and COSMO-RS solubility predictions, 2-butanol and isobutyl acetate were chosen for further investigation based on maximum solids loading and theoretical volumetric throughput.

Seeded cooling crystallisation experiments were performed on the Crystalline platform with both systems forming bimodal product crystals of 50 μm and 10–20 μm in size; likely due to the grinding effect of bottom stirring. The crystals grown in 2-butanol had a more plate like morphology than the more needle-like isobutyl acetate product. Both systems were very slow growing with lower yields for 2-butanol (31.6 % and 31.3 %) than isobutyl acetate (44.5 % and 45.1 %) after 230 min. Seed loading for these experiments was 10 % of total API.

Scaling up the experiments to the EasyMax platform to assess growth kinetics and mixing under more representative conditions resulted in similar yields (2-butanol = 33.9 % and isobutyl acetate = 43.8 %) and particle habit. The 2-butanol formed an unstirrable paste for the first experiment but did not when the experiment was repeated. Some agglomeration was also observed in the 2-butanol system. Product size distribution was unimodal with D_{50} of 40 μm.

In order to improve the yield, new seed was prepared using a high shear wet mill to increase the surface area for growth reducing D_{50} from 30 to 10 μm. Easymax experiments were repeated using this new seed material, as well as the implementation of a quadratic temperature profile over four hours to maintain a constant *SS* (1.5 for isobutyl acetate and 1.96 for 2-butanol). An unstirrable paste was again formed in the 2-butanol system so 2-butanol was not considered further for this process due to operating risks of paste formation and agglomeration likelihood. The isobutyl acetate system afforded a yield improvement from 43.75 % to 48.72 %. This experiment was then repeated and held overnight, where the yield increased to 88.55 %. Growth rate with this four-hour quadratic profile was measured at 0.25 μm/min.

3.4.2. AZD0837 Stages 6–10

Stage 6: A series of growth parameterisation experiments were performed to parameterise a model for a cooling crystallisation of AZD0837 in isobutyl acetate. Even though the isothermal desupersaturation experiments were performed at very high supersaturations, no change in the concentration was observed in all experiments except the high concentration/supersaturation experiment. The growth rate constant and activation energy showed high correlation, and it was found that secondary nucleation is negligible in the system (growth rate constant = $1.61x10^{-11}$m/s, supersaturation order = 1.46 and activation energy = 6383 J/mol).

A Bayesian led design of experiments (DoE) was implemented using BayBE (Merck, 0.13.0, (GitHub, 2025)) with the objective of minimising the process mass intensity (PMI) with feed concentration (21 wt%) and seed size (20 μm) set as fixed parameters constrained within the QbDD stage 2 criteria. Experimental conditions suggested by BayBE were simulated in G-PROMS using the estimated kinetic parameters. The PMI values derived from these simulations were incorporated into the BayBE model to inform a total of 8 *in silico* experiments. Four validation experiments were carried out to refine the model parameters at the optimised supersaturation (growth rate constant = $3.03x10^{-10}$m/s, supersaturation order = 3.28 and activation energy = 45061 J/mol) and the revised model showed adequate goodness of fit when comparing the χ^2 (chi-squared) value of 120.2 as compared to χ^2 critical of 124.4 (table 7).

AZD0837 exhibits slow growth only and due to the long residence times required to meet the desired criteria, gPROMs model evaluation of different crystallisation scenarios was carried out constrained within a University laboratory environment restricted total run time) and a batch crystallisation process was identified as optimal with quadratic cooling to maximise the supersaturation.

Stages 7–9: With slow growth rates and no significant other rate processes, no significant quality risk items were identified beyond the requirement of solvent levels in the final product and that will be assured by testing. Risks were however identified for manufacturability and sustainability targets. Yield was identified as a key performance indicator due to the slow growth kinetics with process optimisation efforts were focused on meeting the yield and flow function targets. It was accepted that smaller particle size than desired would result from the need to increase seed surface area to maximise the yield.

Model predictive control (MPC) was implemented to minimise batch-to-batch variability and to maximise growth rates (yield) and minimise reaction time by keeping supersaturation constant. Control of the supersaturation setpoint was achieved by applying a cascade control loop. Temperature and concentration were measured using a PT-100 temperature probe and UV probe, respectively. Both measurements feed the calibration model for concentration prediction which calculated the supersaturation based on the MSZW curve. This supersaturation value was then passed through a supersaturation model predictive controller which adjusted the reaction temperature controller to maintain the calculated supersaturation value (or regain it if lost). The temperature control model was built by conducting a series of dynamic step tests, where a series of pseudo-random temperature setpoint changes are automatically applied to the vessel water jacket. Next, the resultant process response is used to automatically develop a “dynamic” process model, which is then incorporated into a “setpoint tracking” predictive controller. A detailed description of this will be published.

Stage 10: The validation run was carried out in a standard 1 L Radleys jacketed vessel equipped with baffles, operating at an agitator speed of 300 rpm. Supersaturation control was effectively maintained, with seed addition occurring after a controlled cooling phase from 82 °C to 53 °C. Concentration monitoring and supersaturation control were achieved using an in-line UV probe, with loading space standardisation (LSS) applied to account for the effects of temperature in the UV spectra (Chen et al., 2005; Chong et al., 2022). Following crystallisation, the final product was filtered under vacuum and washed with heptane. Drying was performed in a vacuum oven at 40 °C for 24 h prior to analysis. The results (Table 7) show a good fit with the model prediction (X^2 being lower than X^2 −critical) and process having excellent sustainability metric of high solids loading at end of crystallisation of 26 wt % and a PMI of just above 6.

4. Discussion

4.1. Process objectives

Quality targets.

All 3 compounds met the required quality criteria, which was a fundamental aim of the approach.

Manufacturability and sustainability targets (see section 2.2).

Good manufacturability targets were achieved for all 3 compounds for the flow function coefficient, and for ibuprofen and lamivudine for particle size. Due to the slow growth rates of AZD0837, we were unable to meet the desired manufacturability target (to match typical excipient PSDs) for particle size, although this could have been met with longer residence times and a lower seed loading.

Acceptable yields were obtained for all 3 compounds, and these could have been increased with approaches such as longer residence times, mother-liquor recycling and recropping. Solid mass fractions and PMIs for the crystallisation were aspirational for AZD0837, good for ibuprofen and acceptable for lamivudine. Lamivudine was limited by the need to control water activity coefficients and ibuprofen by risks of fouling and encrustation when driving higher anti-solvent levels and the resultant solids loading. Similar PMIs across the 3 compounds were achieved for the isolation steps. Residence times were restricted due to constraints of working in a university laboratory, but could easily be extended in a commercial setting when operating over multiple days or weeks also minimising the impact of process start-up and shut-down.

The inter-dependencies of the various targets mean that compromises are often made for manufacturability and sustainability targets within practical constraints and the workflow helps ensure decisions are made collaboratively and in a rational, explicit manner. Lamivudine and AZD0837 were straightforward for a model-based approach to find conditions that best met the multi-objective criteria. For Ibuprofen, however, the small scale experiments and associated risk assessments identified several risk factors (agglomeration, seed size) that would normally have been addressed, removed or alternate process choices made to avoid them as part of process development. To challenge the workflow, we deliberately ran with large seed sizes and a solvent system that resulted in agglomeration resulting a final process that would not be commercially optimal. Several iterations and relaxations of the desired criteria (sustainability and manufacturability) and process constraints were required to find viable conditions that best met the desired criteria. Introduction of digitally supported multi-objective decision making would improve this in the future. The use of GSA helped to identify the highest impact parameters and it is estimated, compared to previous traditional approaches, that this saved several weeks of experimental work.

Table 7
Comparison of predicted and actual results from AZD0837 validation run.

Material	Particle Size (μm, Morphologi 4)			Process Mass Intensity (Solid % in final slurry)	Isolated Yield (%)
	D_{10}	D_{50}	D_{90}		
Seed	12.9	33.4	72.1		
Final slurry	134.9	86.93	226.3		
Isolated product	33.9	80.7	203.9	6.16 (26.1)	92.5
Model predicted	31.3	75.1	190.2	6.11 (26.4)	93
X^2	120.2				
X^2 − Critical	124.4				

Note: X^2 and X^2-critical values relate to the goodness of fit of the model at stage 6 used to design the validation run.

4.2. Quantification of benefits

Collation of Data for Quantification of Benefits: We have compared the 3 processes described in this paper to 3 previously published studies carried out at similar scales for proving runs in CMAC; paracetamol (Brown et al., 2018), lovastatin (Brown et al., 2024) and mefenamic acid (Urwin et al., 2023). In addition, we have reviewed 4 confidential projects run on pharmaceutical compounds in active development where the QbDD workflow approach was applied. The amount of material used and the number of experiments (as a proxy measurement for resources) were collated.

Further assumptions taken to enable fair comparison were: a) solvent screening experiments caried out in a Crystalline® platform count as 1 experiment although 8 experiments were carried out simultaneously; b) best efforts have been made to align experiments to QbDD stages for those compounds investigated before the workflow was developed; c) where available, amounts of material and number of experiments reported in the published literature experiments were counted, and, where not published, equivalent experimental data were gathered from electronic lab notebooks.

Comparison of Processes for Quantification of Benefit: Quantification of the benefit of different ways of working in the process development of new compounds is challenging. Direct comparison cannot be made between approaches as there are different levels of complexity or business requirements for the different compounds. To address this, the research team with an independent academic reviewed the processes and, using on expert opinion, assigned the processes a nominal complexity score of high (H), medium (M) and low (L) based on the number of process steps, number of physical rate processes occurring and any additional complexity such as the requirement for impurity rejection or mother liquor recycle. The amount of material in the confidential projects is often defined by the number of repeats required for proof of robustness and we have normalised these values as if only 1 proof of concept run was required.

A summary of this data is shown in Table 8: Comparison of amount of material and number of experiments used in process development pre- and post-application of QbDD workflow. Two compounds (Ibuprofen and confidential project C) in the QbDD section show high levels of material use in Stages 6–10; this was due to higher levels of non-modelled and modelled phenomena that were sensitive to hydrodynamic changes requiring larger scale experiments. More detailed evaluation of the models for sensitivity to hydrodynamic changes (e.g., incorporation of a shear term in the kernel of an agglomeration model) coupled with improved characterisation of the equipment using computational fluid dynamics would have reduced the amount of material and experiments required. From Table 8, 3 processes (paracetamol, lovastatin and mefenamic acid) that were developed pre-QbDD workflow were compared with 4 processes (lamivudine, ibuprofen and confidential projects A and C) that were developed using the QbDD workflow. Lamivudine was not included in this comparison as the process was too simple to compare to non-QbDD process examples (Table 9).

Table 9 shows a significant reduction in both material usage (52–65 %) and the required number of experiments (28 %) when the QbDD

Table 8
Comparison of amount of material and number of experiments used in process development pre- and post-application of QbDD workflow.

QbDD Stage		Mass of material used (g)			Total Mass in g (Excl proof run)	Total Mass in g (1 proof run)	Number Lab Expts			Total Expts	Complexity (High, Medium, Low)
		1–5	6–7	8-10[a]			1–5	6–7	8-10[a]		
pre-QbDD Worflow	Lovastatin	780	2000	350	2780	3130	12	18	2	32	H, conti AS cryst + spherical agglomeration
Using QbDD Workflow	Paracetamol	165	1950	3700	2115	3348	23	23	1	47	M, conti cooling cryst + 3 equipment types compared + multiple runs
	Mefenamic Acid	87	937	295	1024	1319	14	32	1	47	H, wet mill seed + conti AS and cooling cryst
	Lamivudine	29	138	404	167	571	9	6	1	16	M, conti cooling cryst + polymorph control
	Ibuprofen	123	1393	542	1516	2058	12	17	1	30	H, agglomeration + hydrodynamically sensitive + conti AS and cooling cryst
	AZD0837	99	129	54	228	282	7	5	1	1	L, batch cooling cryst
	Confidential Project A	110	475	1100	585	1685	19	27	3	49	H, mechanistic model + seed response expts + morphology screening + 3 point solubility check
	Confidential Project B	55	100	250	155	405	6	26	1	33	M, narrow MSZW, ppt and oiling out
	Confidential Project C	55	1050	500	1105	1605	6	23	1	30	H, diastereomeric impurity reject, ML recycle
	Confidential Project D	50	425	1200	475	715	5	15	6	26	M, conti pH switch, Taylor-Couette, 5 batches for stage 10

NOTE: Projects A-D were confidential projects and compound cannot be disclosed, conti = continuous, expts = experiments, cryst = crystallisation, AS = anti-solvent, ppt = precipitation, ML = mother liquor.

Table 9
Quantification of the benefits of applying the QbDD workflow to comparable processes. Data were averaged for processes developed without (pre-QbDD) and with the QbDD workflow.

	Mass of material used for QbDD stages 1–8	Mass of material used for QbDD stages 1–10 with 1 proof run	Total number of experiments for QbDD stages 1–10
Pre-QbDD process average[a]	1973 g	2599 g	42
QbDD process average[b]	686 g	1257 g	30
% Reduction for QbDD workflow	65 %	52 %	28 %

a. paracetamol, lovastatin and ibuprofen; b. lamivudine, ibuprofen and confidential projects A and C.

workflow was applied when comparing similar processes for development of crystallisation, isolation and drying processes. These reductions have been achieved by leveraging digital twins and simulations to explore a digitally augmented design space virtually, minimising the need for physical trials. The use of GSA has supported multi-objective decision making, especially where many of the desired criteria could not be met within the physical or business constraints. Careful design of small-scale experiments allows for efficient parameterisation of physics-based models and identification of potential risks at this scale enable targeted experiments for non-modelled phenomena evaluation.

4.3. *Learnings from implementation of workflow*

The substantial improvements outlined above have been driven by a change in philosophical approach, ways of working, improvement in deployment of digital tools, and a clear focus on delivering against defined whole process objectives whilst assuring quality in keeping with the ethos of QbDD (Mustoe et al., 2025).

The application and evolution of the workflow provides a science driven, rational structure for a multi-location, multi-disciplinary team to work more efficiently and effectively together with model driven decision making. The emphasis on model parameterisation and identification of non-modelled phenomena from ensured pre-existing assumptions about experimental design were challenged leading to significant reductions in the scale of many experiments. Conversely, it has also highlighted the importance of addressing phenomena such as nucleation or agglomeration that are scale and equipment sensitive and hence require further development of science of scale tools. The characterisation of the agglomeration kinetics of ibuprofen required re-parameterisation of models when changing the scale or equipment; the scale of the effect was larger than anticipated and the risk could have been evaluated using computational-fluid dynamics modelling.

The value of simulation and model prediction is clear from this work and this workflow provides an approach to overcoming the digital skills gaps required to deliver the benefits from Pharma 4.0 (Baxendale et al., 2015; Department for Business and Trade, 2017; Partnership, 2023; Singh, 2024). The improvement in digital skills outlined here, does not require everyone to be able to develop, parameterise and run process models, but that they must be aware of what a model can (and can't) do, what the required inputs are and how they impact the process. Understanding of how inputs and outputs to models relate to practical phenomena and process parameters was crucial to the practical implementation and realisation of the benefits. Spending time mapping these handshakes at the start of the project as a multi-disciplinary team significantly improved understanding, teamworking and was crucial for the approach alongside targeted skills training.

The work has been carried out by different groups and the workflow is not prescriptive about what predictive process models must be used

when, so there is variability between the examples. The workflows were informed and developed during the case studies and so have evolved. As further domain knowledge and improved models are incorporated increasing the coverage of relevant phenomena, this generalised workflow will also deliver more consistent data sets enabling further development and validation of predictive models. Automation of the material property predictions in electronic laboratory notebooks is also recommended to democratise the use of these tools.

As is clear for example from the ibuprofen study, model performance is varied for different processes at present. It remains important to have clear criteria in place to assess model performance, uncertainty and suitability to guide effective use (Kuemmel et al., 2020; O'Connor et al., 2024). The comprehensive use of global systems analysis and sensitivity analysis provides material, resource and experimental saving insights for process optimisation and model-informed decision making. By identifying the dominant sources of uncertainty, from operational or kinetic parameters, we can implement better control strategies for the most influential factors. This approach allows us to mitigate risks and more consistently achieve the desired project objectives.

4.4. Areas for future research

QbDD is a rapidly evolving field and this work highlights several areas for further development including: (a) incorporation of multi-objective, systems-level optimisation and decision making; (b) use and exemplification of different model types including generative AI, machine learning and hybrid; (c) improved evaluation of non-modelled phenomena at smaller scale; (d) improvement of physics-based (or mechanistic) models containing multi-phase complex systems, e.g., agglomeration; (e) expansion and improvement of models to take account of more non-modelled phenomena; and f) mapping of the handshakes between model functions (inputs and outputs) and practical process parameters.

Consideration of quality and regulatory requirements when developing models from the start is crucial and incorporation of the principles laid out in ASME V&V40 and the recent FDA discussion document on AI for medical devices and drug and biological products as a standard way of working would be very beneficial (O'Connor et al., 2024; U.S. Department of Health and Human Services; U.S. Food and Drug Administration, 2025). Key aspects include question of interest, context of use, defined evaluation criteria (with acceptable uncertainty) and final credibility assessments. The Digital CMC Centre for Excellence in Regulatory Science and Innovation is working to develop a regulatory readiness guidance framework for digital tools and we welcome this development.

5. Conclusions

This paper has demonstrated and quantified the effectiveness of a digitally led approach to process development in drug substance manufacturing using a QbDD workflow. The workflow has been exemplified for the crystallisation and isolation of three APIs representing a variety of material and process challenges from the perspective of control and assuring consistent performance, including agglomeration (ibuprofen), solid state form (in the case of lamivudine), and slow growth rate (AZD0837).

The application of the QbDD workflow resulted in a significant reduction in experimental burden with 28 % fewer experiments and a substantial decrease in material usage, with savings between 52 and 65 %, compared to traditional development approaches. These improvements were enabled by scaling down experiments, astute model parameterisation, and integrating global system analysis and sensitivity analysis within a digitally augmented design space. Importantly, the workflow operated within realistic process constraints and aligned with clearly defined project objectives. Thus, the workflow improves sustainability and decreases the cost of materials required during early development by reducing the amount of material required. The successful use of initial experimental data to inform predictive modelling underscores the importance and the strength of the digital framework in guiding decision-making.

We have demonstrated that a digitally driven, model-informed approach through the QbDD workflow offers a powerful pathway to more sustainable, efficient, and predictive pharmaceutical process development, representing a key step toward the broader digitalisation of CMC.

Declaration of Generative AI and AI-assisted technologies in the writing process

During the preparation of this work the author(s) used ChatGPT-4o in order to help reduce word count in main manuscript only. After using this tool/service, the authors reviewed and edited the content as needed and takes full responsibility for the content of the publication.

CRediT authorship contribution statement

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Declaration of competing interest

The authors declare that they have no known competing financial

interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ijpharm.2025.126343.

Data availability

Data link attached at attached file stage.

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Glossary

ATR: Attenuated Total Reflectance
BCS: Biopharmaceutical Classification System
BPCS: Biorelevant Performance Classification System
CCS: Crystallisation Classification System
CMAC: Future Continuous Manufacturing and Advanced Crystallisation Research Hub
CMC: Chemistry, Manufacturing and Controls
CSD: Cambridge Structural Database
DCS: Developability Classification System
EtOH: Ethanol
FDA: Food and Drug Administration
GSA: Global Sensitivity Analysis
HME: Hot Melt Extrusion HME
ICH: International Council for Harmonisation
IR: Infra-red
MCS: Manufacturability Classification System
MCS+: Manufacturing Classification System plus
MHRA: Medicines and Healthcare products Regulatory Agency
MPC: Model Predictive Control
MSMPR: Mixed Suspension Mixed Product Removal
PMI: Process Mass Intensity
PSD: Particle Size Distribution
PTFE: Polytetrafluoroethylene
QbD: Quality by Design
QbDD: Quality by Digital Design
QbT: Quality by Testing
QTPP: Quality Target Product Profile
UV: Ultraviolet
%: Percentage, or mass fraction percentage when referring to solutions