Multi-objective Dynamic Optimisation of Ampicillin Batch Crystallisation

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Multi-objective dynamic optimisation of ampicillin batch crystallisation

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Abstract

Ampicillin is a key β-lactam antibiotic listed as a World Health Organisation (WHO) *Essential Medicine*. Crystallisation is a unit operation of paramount importance in pharmaceutical manufacturing, whose design and operation are essential in controlling process yield and important product quality attributes, such as mean product crystal size (MCS) and size distribution width. A published model for the solubility of ampicillin as a function of pH as well as growth and nucleation kinetics is used towards the simulation and optimisation of its batch crystallisation. This study performs multi-objective dynamic optimisation of the batch crystallisation of ampicillin to establish optimal pH trajectories for different production objectives, including maximising the mean crystal size whilst minimising the size distribution width subject to various yield constraints. Trade-offs between different product quality attributes are thus quantified, visualised and discussed.

Keywords: Multi-objective dynamic optimisation; batch crystallisation; ampicillin.

1. Introduction

Ampicillin is a broad-spectrum, semi-synthetic β-lactam antibiotic, used to treat various bacterial infections such as urinary and respiratory tract infections, being one of the ten most consumed antibiotics worldwide (Hamed et al., 2015). The β-lactam family of antibiotics are typically delivered orally and hence crystallisation is an essential unit operation in the production of these drugs, including ampicillin. The design and optimisation of crystallisation processes for efficient antibiotic production is important for its lean and agile manufacturing. The final size, shape and form of crystalline products are essential in pharmaceutical manufacturing as these product quality attributes influence downstream operations as well as the bioavailability of the crystalline product. Significant efforts in the development of batch crystallisation processes for their design and control have furthered pharmaceutical crystallisation significantly (Gao et al., 2017). Process modelling and optimisation studies performed before laborious, expensive experimental campaigns can elucidate optimal batch crystallisation manipulations (e.g. temperature, pH, antisolvent dosing) profiles, thus allowing for significant R&D time and cost savings.

The batch crystallisation of ampicillin via pH manipulation has been demonstrated in the literature, including a model with detailed kinetics and solubility behaviour as a function of pH (Encarnación-Gómez et al., 2016). Dynamic optimisation of pH-profiles for ampicillin batch crystallisation may establish improved operating policies for improved process performances vs. straightforward linear pH variations demonstrated in the

literature thus far. This study implements the described ampicillin batch crystallisation model for dynamic optimisation of pH manipulation profiles to optimise product quality attributes subject to different operational and performance constraints. First, the published dynamic model for batch crystallisation is described in detail. The formulation of a dynamic optimisation problem with pH as the manipulated variable is described, with different case studies corresponding to experimental demonstrations. Optimisation results for different considered cases are presented in detail, followed by a critical comparison regarding trade-offs between process performance and key product quality attributes.

2. Batch Crystallisation Model

The ampicillin batch crystallisation model describes the antibiotic's aqueous solubility vs. pH, nucleation and growth kinetics and population and mass balance equations, the simultaneous solution of which describes the crystallisation process (Encarnación-Gómez et al., 2016). It is assumed that all considered processes are isothermal at T = 25 °C, crystallisation is only induced via pH-variation and that pH variation in mixtures are instantaneous upon the implemented manipulation. The solubility of ampicillin as a function of pH is described using the extended Pitzer model (de Pessôa Filho et al., 2008) in Eqs. 1–2, where constants ε, σ, pK_{A1} and pK_{A2} are taken from the literature (Encarnación-Gómez et al., 2016), k_B = Boltzmann constant, N_A = Avogadro number, ρ = ampicillin density and the isoelectric point (pI) and its corresponding solubility (S(pI)) are regressed in previous work (Dafnomilis et al., 2019)

$$\log\frac{S(pH)}{S(pI)} = pI - pH + \log\left[\frac{1+10^{pH-\mathrm{p}K_{A1}}}{1+10^{pI-\mathrm{p}K_{A1}}}\right] + \log\left[\frac{1+10^{pH-\mathrm{p}K_{A2}}}{1+10^{pI-\mathrm{p}K_{A2}}}\right] + \frac{2}{\ln 10}\lambda[S(pI) - S(pH)] \quad (1)$$

$$\lambda = \frac{2\pi\sigma^3 N_A \rho}{3}\left(1-\frac{\varepsilon}{k_B T}\right) \quad (2)$$

Crystallisation kinetics are described by Eqs. 3–7, where J = overall nucleation rate, G =linear growth rate, M = suspension density, SS = supersaturation (all of which are a function of time, t), and parameters k_B, B_0, b, s, k_G and g are found in the literature (Encarnación-Gómez et al., 2016). The population balance in a batch crystalliser is described by Eq. 8, where n = the population density function, L = characteristic crystal length (assuming linear 1D growth), complimented by the boundary (Eq. 9) and initial (Eq. 10) conditions, corresponding to the population density of nuclei at t and that of seeds (n_0), respectively. The solute mass balance across the liquid and solid phases is described by Eq. 11, where the ampicillin concentration, [Amp], removed from solution via crystallisation and contributes to the suspension density (M).

$$G(t) = k_G\,(SS(t)-1)^g \quad (3)$$

$$J(t) = B_1(t) + B_2(t) \quad (4)$$

$$B_1(t) = k_{B1}\exp\left(-\frac{B_0}{\ln(SS(t)^2)}\right) \quad (5)$$

$$B_2(t) = k_{B2}\,M(t)^b\,(SS(t)-1)^s \quad (6)$$

$$SS(t) = \frac{[Amp](t)}{S(t)} \quad (7)$$

$$\frac{\partial n(t,L)}{\partial t} = -\frac{\partial\left(G(t)n(t,L)\right)}{\partial L} \quad (8)$$

$$n(t,0) = \frac{J(t)}{G(t)} \quad (9)$$

$$n(0,L) = n_0 \quad (10)$$

$$\frac{\mathrm{d}[Amp]}{\mathrm{d}t} = -\frac{\mathrm{d}M}{\mathrm{d}t} \quad (11)$$

3. Dynamic Optimisation Problem Formulation

This study considers the dynamic optimisation of the batch seeded crystallisation of ampicillin by manipulation of the pH trajectory over the batch duration. Generally, large Mean Crystal Sizes (*MCS*) and narrow size distributions (i.e., low *STD* or *CV*) are desired. Here, we maximise *MCS* while minimising *STD* by considering the objective function as a weighted sum of *MCS* and *STD* (Eq. 12), with associated weights W_{STD} and W_{MCS}. Imposed constraints on the problem are defined as follows. The first constraint (Eq. 13) ensures sufficient supersaturation at the beginning of the batch. The second constraint (Eq. 14) ensures the pH is not too low (causing ampicillin degradation) or high (forming undesirable non-trihydrate ampicillin polymorphs); ampicillin has limited chemical stability at pH ≤ 5, below which degradation products are formed, and undesired non-trihydrate polymorphs are formed at pH > 8 (Bezerra et al., 2018). The third constraint (Eq. 15) ensures that a minimum of a target amount of ampicillin is crystallised from solution at the end of the batch duration, t_f. The fourth constraint (Eq. 16) ensures sufficient *SS* is maintained. We consider W_{STD} = 1.0, W_{MCS} = 1.5 and the number of equispaced time discretisation intervals in the time domain, N = 30. The number of state variable collocation points, K_x = 3, and the initialisation pH profile is constant $pH(t) = 7$, unless stated otherwise in Section 4; the effects of varying W_i on the objective function and values of N have been considered and analysed previously (Dafnomilis et al., 2019).

$$\min_{pH(t),t_f} f(x, t_f) = W_{STD}STD - W_{MCS}MCS \tag{12}$$

$$7 \leq pH(t_0) \tag{13}$$

$$5.5 \leq pH(t) \leq 8.0 \tag{14}$$

$$[Amp](t_f) \leq [Amp]_{target} \tag{15}$$

$$1 < SS(t) \tag{16}$$

The optimisation problem is solved using orthogonal collocation on finite elements via the DynOpt package in MATLAB (Čižniar et al., 2005), which has been used in previous work for the optimisation of biochemical process control trajectories (Rodman and Gerogiorgis, 2019). We compare dynamic optimisation results for different cases of seed loading. Table 1 summarises parameters considered for each case, corresponding to three (experimentally demonstrated already) seeded ampicillin crystallisation cases. The target crystallisation yields are comparable with experiments (Encarnación-Gómez et al., 2016).

Table 1: Dynamic optimisation problem cases considered.

Case	**1**	**2**	**3**
Seeding (wt%)	1.8	3.0	15.0
$[Amp](t_f)$ (g kg^{-1})	{6.8, 8.0}	{6.8, 8.0}	{6.9, 9.0}
Yield (%)	{39.8, 29.2}	{39.8, 29.2}	{46.4, 52.1}
t_f (min)	250	350	1,500

4. Results and Discussion

Optimal *pH*, nucleation, growth, *SS* and *MCS* profiles for different cases and yields are shown in Fig. 1. For lower crystallisation yields, the general pH manipulation is a drop near the beginning of the batch, followed by an increase and then a drop towards the end; this results in high *SS* at the start, followed by a decrease and then an increase towards the end. The initial high *SS* promotes nucleation; the subsequent lower supersaturation allows nuclei to grow to attain high *MCS* as per the defined objective function. The final increase in *SS* allows further nucleation to increase the yield to meet the target yield. This

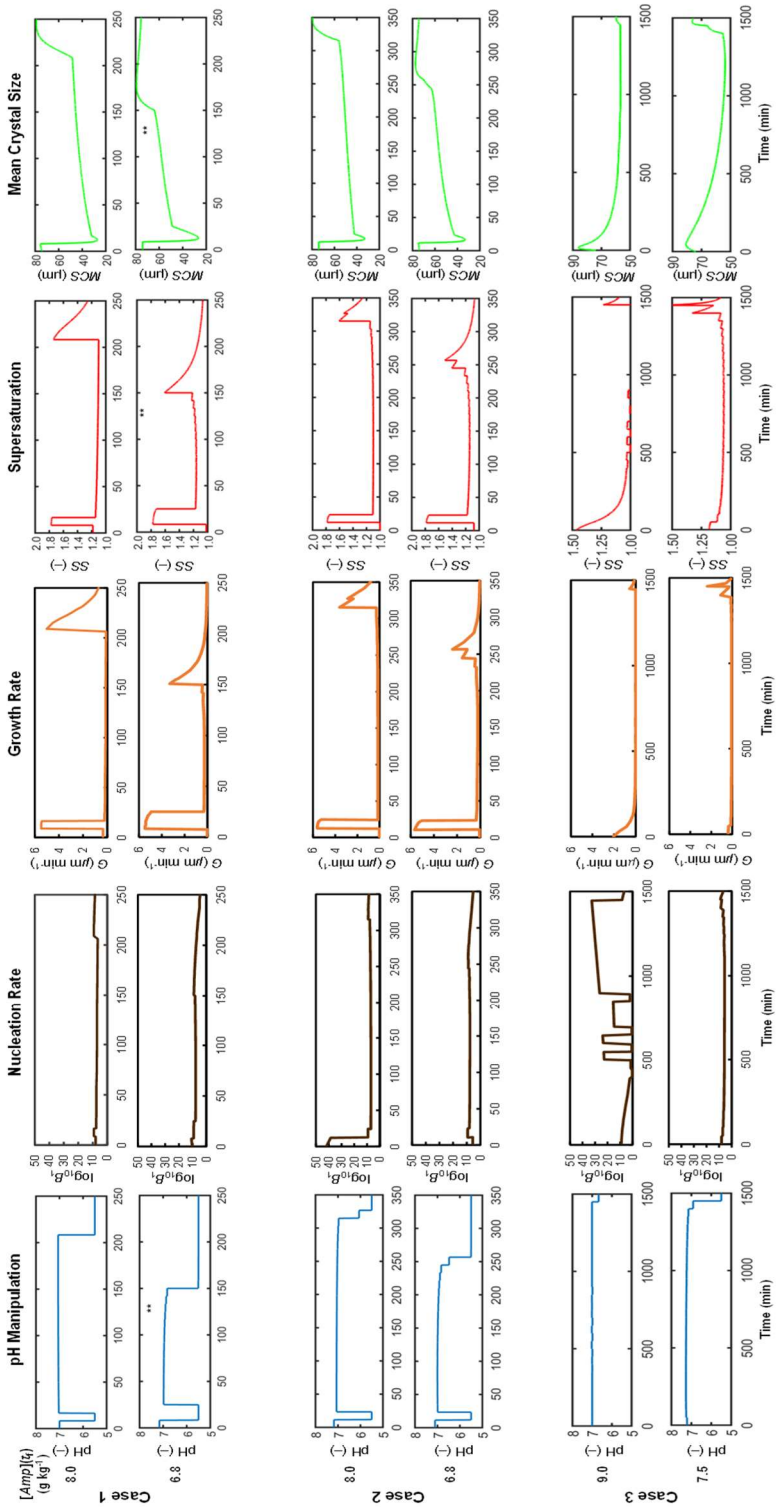

Figure 1: Optimal trajectories for all cases; $N = 30$; $K_x = 3$; initialised at $pH(t) = 7$.

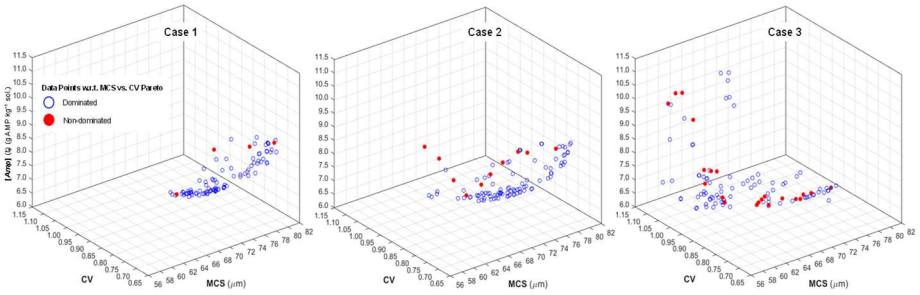

Figure 2: 3D Pareto front of the multiobjective dynamic optimisation problem (all cases).

results in *MCS* profiles which drop at the start (as nuclei form, the average *MCS* decreases) followed by an increase (due to growth dominating). As the target crystallisation yield is increased, the resulting optimal profiles change. The final decrease in pH in order to enhance the yield occurs earlier; this is due to the need to crystallise more nuclei in order to meet the target yield. As a consequence, *MCS* profiles begin to gradually decrease due to the formation of nuclei, although are approximately the same as for lower yields. Lower W_{MCS} values result in similar forms of pH manipulation and state trajectories, with more drastic pH drops resulting in more nucleation, and thus lower final *MCS* values, as *MCS* is given less importance in the objective function (Dafnomilis et al., 2019). As the seed loading is increased, the pH drop towards the end of the batch duration is observed later. For higher seed loading; the yield is enhanced as fewer nuclei are needed to meet the target yield. In all cases, a pH drop is only implemented towards the end of the batch duration, as growth is more important than generating new nuclei.

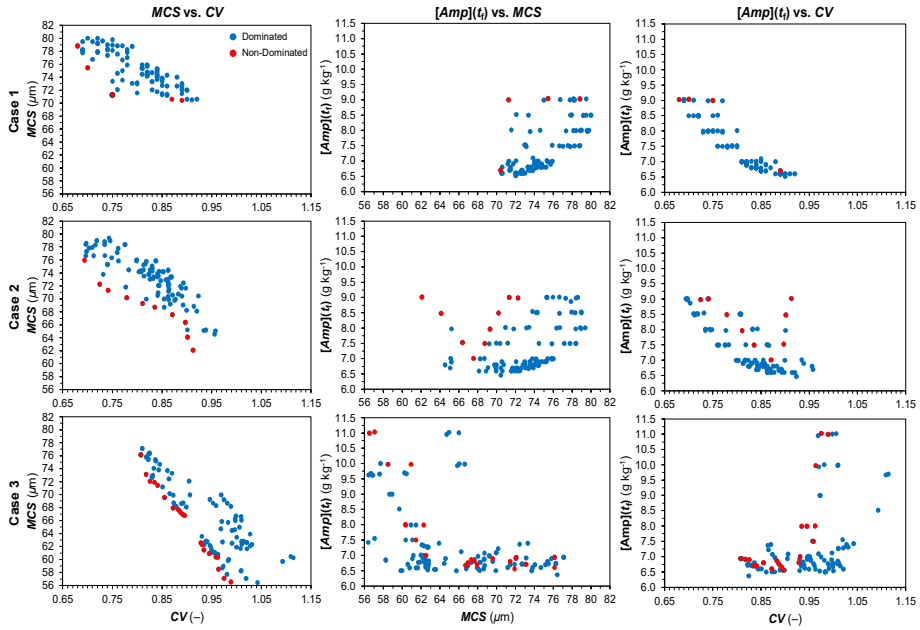

Figure 3: 2D Pareto front projections of the dynamic optimisation problem.

Pareto fronts of [*Amp*](t_f) vs. *MCS* and *CV* are shown in Figs. 2 and 3 to quantify and visualise production trade-offs. For lower seed loadings, the attained *MCS* and *CV* are higher and lower, respectively, than for higher loading. For Case 3, there is not as evident

a trade-off between yield and *MCS* or *CV*. Investigating the effect of intermediate seed loadings and dynamic seeding policies will further elucidate process improvements. While experimental values of *CV* for different seeded cases are not provided in the literature (Encarnación-Gómez et al., 2016), computed *MCS* values attained via dynamic optimisation of pH profiles in this study are higher than reported values, illustrating the benefit of the implemented framework for batch crystallisation process improvements.

5. Conclusions

This study implemented dynamic optimisation for the batch crystallisation of ampicillin via pH control. The dynamic batch crystallisation model encompasses ampicillin solubility behaviour as a function of pH, growth and nucleation kinetics as a function of crystallisation pH, population balances (using the method of moments to reduce their complexity) and solute mass balances. The optimal pH manipulation trajectory varies with target crystallisation yield and considered seed loading. Optimal pH profiles are such that high supersaturation is generated at the start of the batch run in order to meet the target crystallisation yield followed by lower supersaturation to promote growth and minimise the size distribution width. Illustrations of Pareto fronts of target yield vs. product quality attributes (*MCS* and *CV*) show evident trade-offs between the crystallisation performance and desired product size distribution properties. Future work will consider seed loading as a dynamic control variable to further optimise dynamic control profiles to meet different production specifications of ampicillin production.

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