9th International Symposium on Dynamics and Control
of Process Systems (DYCOPS 2010)
Leuven, Belgium, July 5-7, 2010

Optimizing Batch Crystallization Cooling Profiles: The Design of Dynamic Experiments Approach

Andrew Fiordalis and Christos Georgakis [1]

Department of Chemical and Biological Engineering
Systems Research Institute
Tufts University
Medford, MA 02155 USA

Abstract: A new data-driven methodology for optimizing time-variant profiles in batch processes without the need for a first-principles model is applied to a batch cooling crystallization to find the optimum cooling trajectory that minimizes the total amount of nucleation during the crystallization. The method, Design of Dynamic Experiments (Georgakis, 2009), is an extension of the classical Design of Experiments approach and can be applied to any process where time-variant profiles, typically batch and semi-batch operations, are important for optimizing key aspects of the process. As a data-driven approach with no first-principles model required for process optimization, this methodology may be particularly useful for complex processes for which no knowledge-driven model exists.

Keywords: Optimization, Design of Experiment, Batch Crystallization

1. INTRODUCTION

Batch crystallization is an important industrial unit operation, especially in the pharmaceutical and specialty/fine chemical industries where high-value products are produced in small batches. Therefore, it is important to optimize the operating conditions of the crystallization process in order to produce crystals with the desired properties. Optimization also reduces problems with downstream operations, such as filtration, and reduces lot-to-lot variability. Optimization of batch crystallization process can be a difficult task, especially for crystallization systems that exhibit polymorphs, or crystals with geometries that cannot be easily reduced to one dimension, since a more complicated model is required to describe the system.

If a knowledge-driven (first-principles) model for a crystallization process exists, then the process can be optimized, otherwise, a process model must be derived experimentally before optimization can occur. It should be noted that a crystallization model is not a strict first-principles model since nucleation and growth kinetics are typically explained by an empirical relationship whose parameters must be estimated from experiments. Batch crystallization processes can also be optimized using a data-driven model generated via the classical Design of Experiments (DoE) approach. The major drawback of the DoE approach is the inability to systematically evaluate dynamic profiles (i.e., cooling profile, flow profile, or supersaturation profile). Dynamic profiles are an important aspect of batch process optimization as optimal control trajectories typically change with time during the batch.

Temperature is an inexpensive variable to measure and easy to control, therefore, cooling profile optimization for batch crystallizers is a well-studied area. However, in order to determine the optimum cooling trajectory, a knowledge-driven model of the process is required. Choong and Smith (2004) optimized temperature profiles for the batch cooling crystallization of citric acid in water. Worlitschek and Mazzotti (2004) optimized the temperature profile for the batch cooling crystallization of paracetamol in ethanol with the final particle size distribution defined as the control objective. They also verified their simulated results experimentally. Hu et al. (2005) and Sarkar et al. (2006) optimized the temperature profile for a simulated, seeded batch cooling crystallization of potassium sulfate in water.

In each of these papers, relatively simple crystallization models are used in the optimization algorithm. Each model consists of a one-dimensional population balance equation (PBE) coupled with a mass balance equation. Similar assumptions are made in each model: 1) size-independent growth; 2) no crystal agglomeration or breakage; 3) a nucleation rate equal to the sum of the primary and secondary nucleation rates, and; 4) a perfectly mixed crystallizer with crystals homogeneously distributed and no crystal accumulation on the bottom of the crystallizer.

Ma et al. (2002) optimized the cooling profile for a potassium dihydrogen phosphate (KDP) crystallization in water. KDP is a needle-shaped crystal that is described by the crystal length and width. A two-dimensional PBE model was required to perform the optimization. This model was slightly more complicated than the one-dimensional models discussed earlier since an additional growth rate term was required for the second dimension, but the model still neglects crystal breakage, which was shown by Sato

[1] Corresponding Author: *christos.georgakis@tufts.edu*

978-3-902661-69-2/10/$20.00 © 2009 IFAC

10.3182/20100705-3-BE-2011.0163

et al. (2008) to be an important consideration in a KDP crystallization model for crystals with high aspect ratios.

Batch antisolvent crystallizations are even more difficult to model and, thus, optimize. Woo et al. (2006) performed an antisolvent crystallization optimization which required the use of a computational fluid dynamics (CFD) model to properly simulate the solvent-antisolvent mixing that occurred. Nowee et al. (2008) and Trifkovic et al. (2008) mentioned the need for detailed solute-solvent-antisolvent equilibrium data and kinetic parameters for the growth and nucleation mechanisms in the solvent-antisolvent system. This data is usually not readily available. An additional layer of complexity is introduced to these models when the system includes agglomeration and breakage and/or crystal polymorphs.

In this paper, we look at optimizing the cooling profile for a batch crystallization using no prior knowledge of the crystallization process. In the literature cited above, an optimization of this nature typically requires *a-priori* knowledge of the crystallization system and a detailed first-principles model. Model formulation can be difficult, especially when dealing with systems that have more than one internal coordinate to track in the PBE and where agglomeration and breakage occur or if the crystallization system has one or more polymorphic forms.

Additionally, we apply a new methodology, Design of Dynamic Experiments (DoDE), to a batch crystallization model and show how a time-variant cooling profile can be optimized without a knowledge-driven model. It should be mentioned that the DoDE methodology is not meant to replace first-principle models, rather, it is meant to provide a means of optimizing dynamic profiles for batch processes lacking a detailed, knowledge-driven model.

2. DESIGN OF DYNAMIC EXPERIMENTS

The Design of Dynamic Experiments methodology was introduced recently by Georgakis (2009). The method is an extension of the classical Design of Experiments approach. The classical DoE approach allows for experiments to be designed based on the number of factors (variables) being considered and the number of levels (values) each factor can assume. The factors in a DoE design are static, meaning the factor can only describe one value over the course of an experiment. The static nature of the classical DoE method is a major limitation when designing experiments for systems where a dynamic profile is preferred over a static value for one or more of the factors under study.

Design of Dynamic Experiments allows for the systematic evaluation of time-varying profiles in the experimental design through the use of dynamic factors. These dynamic factors, along with any static factors considered in the experiments, can be used to create a response surface model (RSM), which can then be optimized. The optimum values of the dynamic factors then provide the optimal dynamic profile(s) for the system being studied. The key strength of the DoDE methodology is its ability to determine the optimum dynamic profile(s) for a system without a detailed, knowledge-driven model.

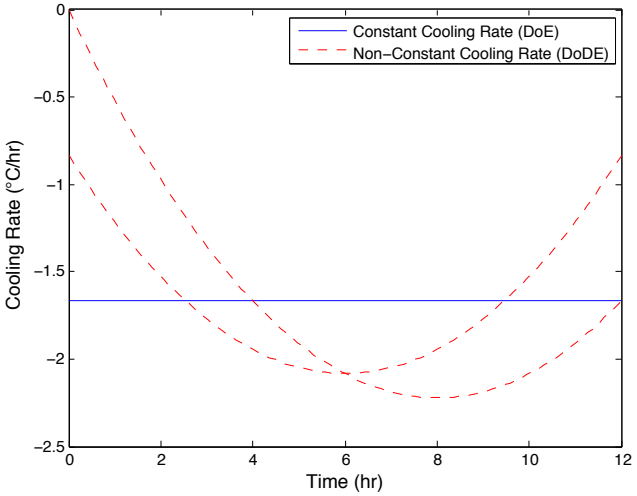

Fig. 1. Examples of possible cooling rates using the DoE and DoDE methodologies. DoE can only evaluate constant cooling rates whereas DoDE can evaluate any constant or non-constant cooling rate profile.

As an example, consider the cooling rate for a batch crystallization. In the classical DoE approach, only constant (static) cooling rates can be considered. The DoDE approach improves upon the DoE methodology by introducing dynamic factors that allow for non-constant cooling rates to be incorporated into the experimental design. (See Fig. 1 for a comparison of cooling rate profiles achievable using DoE and DoDE.) The constant cooling rates from the classical DoE approach give rise to linear cooling profiles. The non-constant cooling rates from the DoDE approach yield nonlinear cooling profiles. These nonlinear profiles can correspond to controlled cooling (profiles concave down) and natural cooling (profiles concave up) (Davey and Garside, 2000) and are similar to the optimum cooling profiles obtained from the optimization of a knowledge-driven crystallization model (Worlitschek and Mazzotti, 2004; Hu et al., 2005; Sarkar et al., 2006).

Non-constant cooling rates are introduced into the DoDE experimental design via a parameterized set of orthogonal polynomials; in this case, the shifted Legendre polynomials. The parameters in the polynomial represent the dynamic factors. The values of the dynamic factors control the shape of the polynomial curve, which represents the cooling rate profile.

The cooling rate profile in this study was constructed from the first three shifted Legendre polynomials. These polynomials were selected as they represent a simple set of orthogonal functions. Two dynamic factors, a_1 and a_2, are multiplied in front of the second and third polynomial components, respectively, to give a cooling rate described by (1).

$$\frac{\mathrm{d}T}{\mathrm{d}\tau} = \frac{T_f - T_0}{t_c}[1 + a_1(1 - 2\tau) + a_2(1 - 6\tau + 6\tau^2)] \quad (1)$$

Where T is temperature (°C), T_0 and T_f are temperatures at the beginning and end of the batch, respectively, t_c is cooling time (hr), and τ is non-dimensional time (t/t_c).

The design space for the dynamic factors was determined by placing constraints on the cooling rate. For the set of

experiments used in this paper the following constraints were used:

(1) The temperature profile must be monotonically decreasing throughout the crystallization.

$$\frac{dT}{d\tau} \leq 0 \tag{2}$$

(2) The cooling rate at the beginning and end of the crystallization cannot be greater than the linear cooling rate.

$$\frac{dT(0)}{d\tau} \geq -1 \tag{3}$$

$$\frac{dT(1)}{d\tau} \geq -1 \tag{4}$$

It should be noted that in an industrial setting the cooling rate constraints would be set by the capacity of the cooling system. We chose our profiles to start within the linear and controlled cooling regime as these profiles tend to minimize the amount of nucleation in a seeded batch crystallizer due to the lower supersaturation values generated by the slower cooling rates at the beginning of the crystallization (Davey and Garside, 2000).

By placing constraints (2)-(4) on the cooling rate (1), the following inequalities are found in terms of the dynamic factors.

$$a_1 - a_2 \geq 0 \tag{5}$$

$$-a_1 - a_2 \geq 0 \tag{6}$$

$$-a_1 + a_2 \geq -1 \tag{7}$$

$$a_1 + a_2 \geq -1 \tag{8}$$

The inequalities are plotted as lines in Fig. 2 and the intersection of the equalities related to these four lines bound the design space of the dynamic factors that produce the desired temperature profiles. The solid circles in Fig. 2 represent the nine experimental points for a two-factor (a_1, a_2) three-level full factorial design. Fig. 3 depicts five of the nine temperature trajectories. Note that all nine temperature trajectories are bound from above and below by the $(-0.5, -0.5)$ and $(0.5, -0.5)$ profiles, respectively.

We now apply the DoDE technique to a batch crystallization simulation and show how the method can be used to optimize a dynamic cooling profile without the use of a first-principles model.

3. CRYSTALLIZATION SIMULATION

The experimental results in this paper were simulated using a paracetamol crystallization model reported by Worlitschek and Mazzotti (2004). The crystallization is simulated in a seeded batch crystallizer. The model assumes that only secondary nucleation and size-independent growth occur within the crystallizer. A one-dimensional, homogeneous PBE is used to model the system and is solved using the Method of Moments (MOM) technique. Each experiment simulated a 15-hour seeded, paracetamol batch crystallization with cooling times that ranged from 12-14 hours. In order to add variability to the data, a 2% normally-distributed random error (multiplicative) was added to the zeroth moment at the end of each simulated experiment.

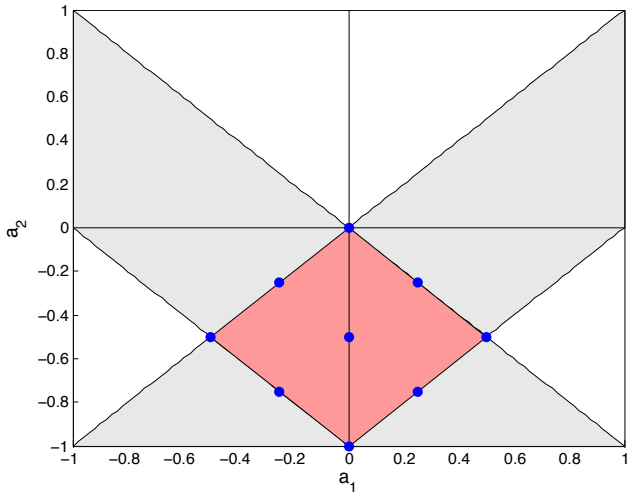

Fig. 2. Design space for the dynamic factors, a_1 and a_2, shown as the intersection of the four inequalities given by (5)-(8). Closed circles represent experimental points.

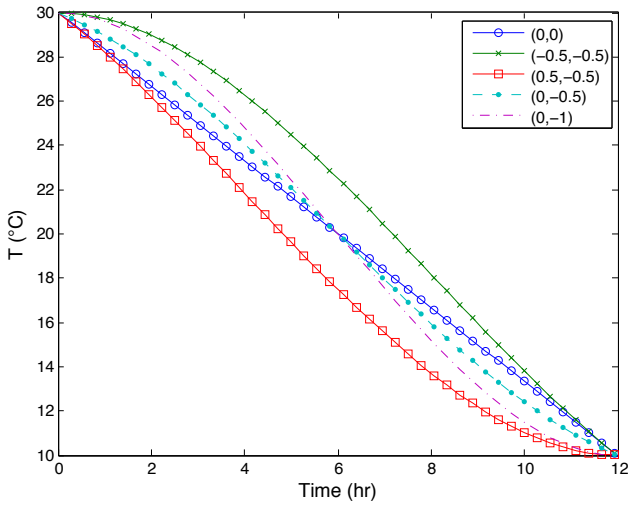

Fig. 3. Temperature profiles for different values of (a_1,a_2) inside the design space. All profiles meet the constraints set by (2)-(4). The linear cooling profile (constant cooling rate) is marked with open circles for reference.

4. RESULTS

We now illustrate how the Design of Dynamic Experiments methodology improves upon the classical Design of Experiments method and show how DoDE is able to find an optimal, nonlinear cooling trajectory for a seeded paracetamol batch crystallization without the use of a first-principles model.

In order to compare DoDE to the classical DoE approach, there must be at least one static factor that is shared between the two design methods. We chose cooling duration, t_c (hr), as the static factor. Three cooling times were evaluated: 12, 13, and 14 hours. The cooling time was defined in terms of the coded variable, a_3, as $t_c = 13 + a_3$ where $a_3 = \{-1, 0, 1\}$. The 13-hour cooling time with a constant cooling rate was considered to be the base case

crystallization scenario for which all subsequent DoE and DoDE results are compared.

The cooling profile was optimized by minimizing the amount of secondary nucleation during the crystallization. In terms of the moment equations, we monitored the zeroth moment (m_0), which represents the total number of crystals in the crystallizer at any time. The zeroth moment at the end of the crystallization was taken as the response variable, which was used to construct response surface models for each of the DoE and DoDE designs. The response surface model, along with constraints (5)-(8), were then used to find the optimum operating conditions that minimized the amount of secondary nucleation.

4.1 Classical Design of Experiments

The DoE experiments evaluated one factor, the cooling time. The cooling rate was held constant and the crystallizer was cooled linearly from 30°C to 10°C for each of the three cooling times. When the crystallizer reached 10°C, the temperature was held constant until the batch time of 15 hours was reached, at which point the simulation was terminated. At the end of the crystallization, the value of the zeroth moment was recorded. The total number of crystals at the end of each crystallization are given in table 1. The total number of crystals decreases as the cooling time increases.

Table 1. DoE Results

Batch Time (hrs)	m_0 x 10^{-11} (crystals/m^3)	Improvement (%)
12	2.78	-12.5
13	2.47	0
14	2.26	8.6

An improvement metric was calculated in order to determine how one crystallization compared to another in terms of minimizing the amount of nucleation taking place. The improvement measures the percent reduction in the total number of crystals at the end of a crystallization compared to the toal number of crystals at the end of the base case crystallization. A negative improvement value indicates an increase in the total number of crystals as compared to the base case. Improvement values are listed in table 1. Based on this very simple DoE we are able to improve the crystallization process by 8.6%

4.2 Design of Dynamic Experiments

Design of Dynamic Experiments is an extension of the DoE methodology, therefore, we can use any of the DoE Designs (see Montgomery, 2005) to construct our DoDE experiments. We evaluated three factors in our simulated DoDE experiments. The static factor, a_3, which controls the cooling time, and the two dynamic factors, a_1 and a_2, which control the cooling rate profile. Each of the factors was assigned 3 levels so that a second-order response surface model (RSM) could be fit to the experimental data. A second-order RSM is given by (9):

$$y = \beta_0 + \sum_{\substack{i \\ i=1,2,3}} \beta_i a_i + \sum_{\substack{i \\ i=1,2}} \sum_{\substack{j \\ j=2,3 \\ i<j}} \beta_{ij} a_i a_j + \sum_{i} \beta_{ii} a_i^2 + \epsilon \tag{9}$$

where y is the response variable, β are the model parameters to be estimated, a_i are the independent variables (factors), and ϵ is the model error.

Three experimental designs were evaluated for the simulated DoDE experiments: 1) a 3^3 full factorial design with three center points; 2) a central composite design (CCD) with three center points, and; 3) a D-optimal design with three center points. The center point experiments were added to the designs to estimate experimental error and to test the model for lack of fit. The lack of fit statistic is one method of checking model adequacy.

The 3^3 full factorial design requires the largest number of experiments when compared to a central composite or D-optimal design (see table 3). The extra experiments allow for a more comprehensive analysis of the design space and result in a smaller variance in the predicted model response, but in most cases there are too many experiments required for it to be a time/cost effective experimental design. The central composite design requires fewer experiments since the experiments are only run at the corners and axial points of the design space. The reduction in the number of experiments results in a larger variance in the predicted model response, but if designed correctly, this variance can be minimized.

A graphical representation of the experimental designs for the full factorial and CCD designs are shown in Figs. 4 and 5, respectively. The design space for the full factorial and central composite design was shifted using the following variable substitution with respect to the second dynamic factor, $a_2' = a_2 + 0.5$, where a_2' is substituted into the response surface model for a_2. This substitution was made to make the design points symmetric around the origin of the design space. By doing this, we reduce the number of cross-correlated parameters in the model when compared to the non-shifted design space.

The D-optimal design is a computer-generated design based on an exchange algorithm that selects a group of experiments from the design space and begins exchanging, one experiment at a time, different design points until the optimal design criterion is met (Montgomery, 2005). The optimality criterion for the D-optimal design is to minimize the determinant of the $(\mathbf{X}^T\mathbf{X})^{-1}$ matrix.

$$\min\left(|(\mathbf{X}^{\mathrm{T}}\mathbf{X})^{-1}|\right) \tag{10}$$

where $\mathbf{X}$ is the matrix of regressors. This design criterion (10) minimizes the amount of correlation between the parameter estimates, and, as a result, provides the best estimates for the model parameters for the number of specified experiments in that design space (Montgomery, 2005).

The D-optimal design used for our experiments consisted of 10 experiments, the minimum number of experiments required to estimate parameters for a three-factor, second-order response surface model. A graphical representation of the D-optimal design is shown in Fig. 6.

The D-optimality criterion can also be used to compare the relative efficiency, D_{eff}, of two designs using (11) (Montgomery, 2005):

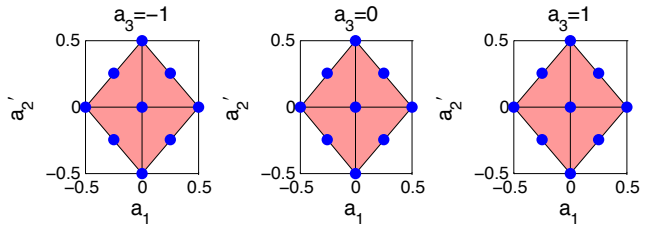

Fig. 4. Graphical representation of experimental points for the full factorial design ($a_2' = a_2 + 0.5$). The same values of the dynamic factors are tested at each level of a_3 in the full factorial design.

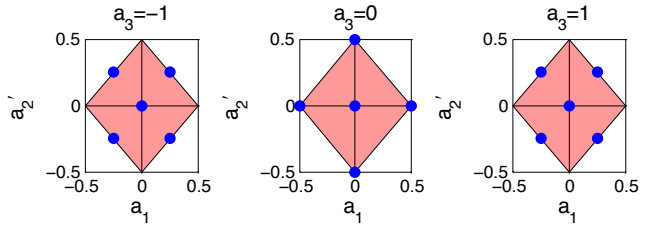

Fig. 5. Graphical representation of experimental points for the central composite design ($a_2' = a_2 + 0.5$).

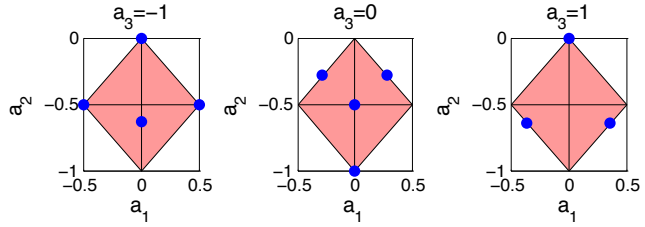

Fig. 6. Graphical representation of experimental points for the D-optimal design.

$$D_{eff} = \left(\frac{|(\mathbf{X}_2^{\mathrm{T}}\mathbf{X}_2)^{-1}|}{|(\mathbf{X}_1^{\mathrm{T}}\mathbf{X}_1)^{-1}|} \right)^{1/p} \tag{11}$$

where $\mathbf{X}_1$ and $\mathbf{X}_2$ are the regressor matricies for design one and two, respectively, and p is the number of parameters in the response surface model.

Comparing the relative efficiencies of the CCD and D-optimal designs to the full factorial design, we see that the CCD is only 46% as efficient and the D-optimal design is only 38% as efficient as the full factorial design. Efficiency is lost as the number of experiments decrease, therefore, the type of design, and thus the precision of the estimated model parameters, must be weighed against the time/cost required to perform the experiments.

Second-order response surface models were fit to the data for each of the experimental designs using linear least squares regression in JMP. All of the models were significant at a significance level of $\alpha = 0.05$. The parameter estimates and 95% confidence interval for each RSM are given in table 2. Parameters with values of zero were found to be nonsignificant.

The lack of fit statistic for the full factorial and central composite design was significant, which indicates that the second-order response surface models might not be the best fit for the data. This result contradicts the results of the residual error analysis (not shown). In all cases, analysis of the residuals showed that they were normally distributed indicating that the models did indeed fit the simulated experimental data adequately. At this point, the best explanation for the significant lack of fit result has to do with how error was introduced to the model. The induced error was proportional to the value of the zeroth moment, but when performing the analysis of variance on the RSM the error is assumed to be additive.

The results of the DoDE experiments are summarized in table 3 along with the results of the classical DoE analysis. The $R^2(adjusted)$ values, which take into consideration the number of factors in the model, are all close to 1, indicating that most of the variability in the system is accounted for by the model. The optimum values for each factor were all found to be in the same area of the design space for all three DoDE designs. The predicted and simulated zeroth moment for each design agree nicely. It is also seen that each optimized case predicts approximately the same number of crystals at the end of each crystallization simulation. This shows that the CCD and D-optimal designs are able to find optimum values close to the values determined from the full factorial design using far fewer experiments. Each of the DoDE designs gave an improvement of approximately 24% over the base case scenario compared to the 8.6% improvement from the classical DoE method. The results of the DoDE analysis give a 17% improvement over the optimum DoE case (14 hours, constant cooling rate). This is an impressive improvement, especially since a first-principle model was not required.

The cooling profile for the optimized DoE and DoDE experiments are show in Fig. 7. It is clearly seen that the optimum DoDE profile is nonlinear. The profile is similar to the profile obtained by Worlitschek and Mazzotti (2004), but an exact comparison cannot be made as we did not have the initial crystal distribution and seed mass used by the authors.

The particle size distributions (PSD) were reconstructed for the optimum DoE and DoDE temperature profiles using a method presented by Giaya and Thompson (2004) (see Fig. 8). In each case the seed crystals grow by the same amount but the amount of nucleation that occurs using the optimum DoDE cooling profile is less than what is produced with the optimum DoE profile. This is due to the nonlinear nature of the cooling profile. The low cooling rate achieved by the DoDE profile at the beginning of the crystallization reduces the initial amount

Table 2. DoDE RSM Parameter Estimates and 95% Confidence Intervals

	3^3 + 3cp* (x10^{-11})	CCD + 3cp* (x10^{-11})	D-opt. + 3cp (x10^{-11})
$\hat{\beta}_0$	2.14 ± 0.0530	2.21 ± 0.0619	2.52 ± 0.0701
$\hat{\beta}_1$	1.06 ± 0.0925	1.07 ± 0.156	1.95 ± 0.531
$\hat{\beta}_2$	0	0	1.44 ± 0.321
$\hat{\beta}_3$	-0.297 ± 0.0327	-0.259 ± 0.0492	-0.311 ± 0.0405
$\hat{\beta}_{12}$	2.19 ± 0.641	2.14 ± 0.881	1.68 ± 1.01
$\hat{\beta}_{13}$	-0.292 ± 0.113	-0.261 ± 0.220	-0.310 ± 0.135
$\hat{\beta}_{23}$	0.114 ± 0.113	0	0
$\hat{\beta}_{11}$	1.91 ± 0.320	1.83 ± 0.520	2.19 ± 0.360
$\hat{\beta}_{22}$	1.54 ± 0.320	1.34 ± 0.520	1.47 ± 0.333
$\hat{\beta}_{33}$	0.0647 ± 0.0530	0	0

*a_2 replaced by a_2' in RSM

Table 3. DoDE Results Summary

Design	# Exp	$R^2(adj)$	Optimum Values a_1	a_2	a_3	$\hat{m}_0 \pm$CI x 10^{-11} (crystals/m^3)	m_0 x 10^{-11} (crystals/m^3)	Improvement (%)
3^3 + 3cp	30	0.977	-0.29	-0.33	1	1.8 ± 0.074	1.87	24.4
CCD + 3cp	17	0.968	-0.30	-0.30	1	1.8 ± 0.12	1.87	24.5
D-optimal + 3cp	13	0.992	-0.23	-0.36	1	1.8 ± 0.087	1.88	23.8
Classical DoE	3	-	-	-	1	-	2.26	8.6

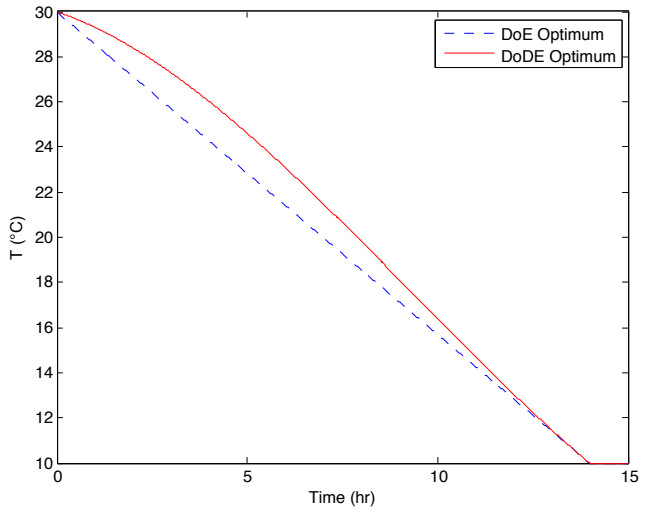

Fig. 7. Optimum cooling profiles from the DoE and DoDE designs. The DoDE method is able to determine optimum nonlinear cooling trajectories.

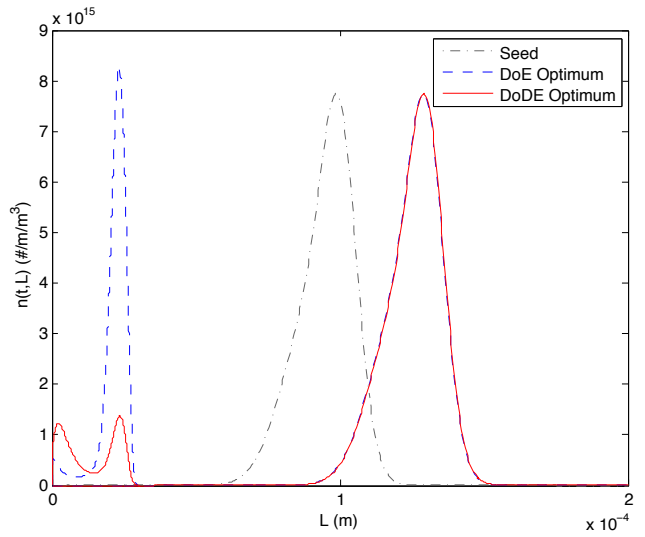

Fig. 8. Reconstructed particle size distributions for the optimal DoE and DoDE cooling trajectories.

of supersaturation in the crystallizer, thus, reducing the total amount of nucleation.

5. CONCLUSIONS

The Design of Dynamics Experiments methodology was applied to a simulated batch crystallization and it was successfully shown that an optimum time-variant cooling profile could be achieved in order to minimize the total amount of nucleation without the need for a first-principles model. This is an important finding for complex crystallization processes for which no knowledge-driven model exists.

The DoDE methodology was compared to the classical DoE approach and was shown to reduce the total amount of nucleation by 17% when comparing the optimum results of the two methods. It was also shown that the central composite and D-optimal designs performed well when compared to the full factorial design. Optimum values for the dynamic factors were found in the same area of the design space in each case and each design improved upon the base case crystallization by approximately 24%.

We are currently applying the DoDE methodology to a concentration-controlled batch crystallization simulation. Preliminary results show that DoDE is able to determine an optimum nonlinear supersaturation trajectory without the use of a first-principles model. An experimental study will be performed to corroborate these findings.

REFERENCES

Choong, K. and Smith, R. (2004). Optimization of batch cooling crystallization. *Chemical Engineering Science*, 59(2), 313–327.

Davey, R.J. and Garside, J. (2000). *From Molecules to Crystallizers: An introduction to Crystallization*. Oxford University Press.

Georgakis, C. (2009). A model-free methodology for the optimization of batch processes: Design of dynamic experiments. IFAC Symposium on Advanced Control of Chemical Processes.

Giaya, A. and Thompson, R. (2004). Recovering the crystal size distribution from the moment equations. *AIChE Journal*, 50(4), 879–882.

Hu, Q., Rohani, S., and Jutan, A. (2005). Modelling and optimization of seeded batch crystallizers. *Computers and Chemical Engineering*, 29(4), 911–918.

Ma, D., Tafti, D., and Braatz, R. (2002). Optimal control and simulation of multidimensional crystallization processes. *Computers and Chemical Engineering*, 26(7-8), 1103–1116.

Montgomery, D.C. (2005). *Design and Analysis of Experiments*. John Wiley & Sons, Inc., 6th edition.

Nowee, S.M., Abbas, A., and Romagnoli, J. (2008). Model-based optimal strategies for controlling particle size in antisolvent crystallization operations. *Crystal Growth and Design*, 8(8), 2698–2706.

Sarkar, D., Rohani, S., and Jutan, A. (2006). Multi-objective optimization of seeded batch crystallization processes. *Chemical Engineering Science*, 61(16), 5282–5295.

Sato, K., Nagai, H., Hasegawa, K., Tomori, K., Kramer, H., and Jansens, P. (2008). Two-dimensional population balance model with breakage of high aspect ratio crystals for batch crystallization. *Chemical Engineering Science*, 63(12), 3271–3278.

Trifkovic, M., Sheikhzadeh, M., and Rohani, S. (2008). Kinetics estimation and single and multi-objective optimization of a seeded, anti-solvent, isothermal batch crystallizer. *Industrial and Engineering Chemistry Research*, 47(5), 1586–1595.

Woo, X., Tan, R., Chow, P., and Braatz, R. (2006). Simulation of mixing effects in antisolvent crystallization using a coupled cfd-pdf-pbe approach. *Crystal Growth and Design*, 6(6), 1291–1303.

Worlitschek, J. and Mazzotti, M. (2004). Model-based optimization of particle size distribution in batch-cooling crystallization of paracetamol. *Crystal Growth and Design*, 4(5), 891–903.