

Dynamic Optimization of a Batch Pharmaceutical Reaction using the Design of Dynamic Experiments (DoDE): the Case of an Asymmetric Catalytic Hydrogenation Reaction

Foteini Makrydaki*, Christos Georgakis**,
Kostas Saranteas ***

* *Systems Research Institute and Chemical & Biological Engineering, Tufts University, Medford, MA 02155 USA (Tel: 617-627-2586; e-mail: Foteini.Makrydaki@tufts.edu).*

** *Systems Research Institute and Chemical & Biological Engineering, Tufts University, Medford, MA 02155 USA (Tel: 617-627-2573; e-mail: Christos.Georgakis@tufts.edu)*

*** *Sepracor, Inc., Chemical Process Research and Development, Sepracor Inc., Marlborough, MA 01752 USA (Tel: 508-357-7655; e-mail: Kostas.Saranteas@sepracor.com)*

Abstract: The present research work aims to demonstrate the effectiveness of the new methodology of Design of Dynamic Experiments (DoDE) in optimizing an important pharmaceutical reaction. An easily developed response surface model (RSM) is used instead of a hard to develop knowledge-driven process model. The DoDE approach allows the experimenter to introduce dynamic factors in the design, which during the RSM optimization are treated as all the other factors, simplifying the analysis significantly, leading to the rapid optimization of batch processes with respect to time-varying decision variables. The DoDE approach enables the discovery of optimal time-variant operating conditions that are better than the optimal time-invariant conditions discovered by the classical Design of Experiments (DoE) approach. In the present case of the asymmetric catalytic hydrogenation, 24 experiments are conducted for the DoDE approach and the best run results in a 45% improvement comparing to the best run of 17 runs of the DoE approach. This is achieved by applying a decreasing temperature profile during the batch reaction. Optimization of the economic performance index of the process through the respective response surface models defines an optimum operation. The DoDE optimum operation is better than the respective one through the DoE. The DoDE advantage increases as the required quality level for the final product is higher. For the medium quality, the DoDE approach results in an improvement of 30% over the DoE one.

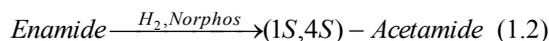
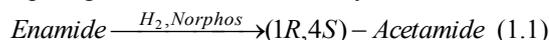
1. INTRODUCTION

The development of a new batch pharmaceutical process, like the asymmetric catalytic hydrogenation, takes place under severe time limitations. Typically the initial process is not quite optimal and continuous improvements are required over the life of the process (Pisano, 1996, 1997). Consequently such processes are initially far from being optimized unless a systematic Design of Experiments (DoE) plan has been executed. However the classical DoE approach does not consider time-varying conditions during the batch process, such as the operating temperature, the co-reactant semi-batch feeding flow rate or the cooling rate in crystallization, among many others. On the other hand, the existing methods for optimal design of dynamic experiments require a model for the process (Espie and Macchietto, 1989). The present paper will examine the use of the recently developed Design of Dynamic Experiments (DoDE) (Georgakis, 2008, 2009) in an important batch industrial catalytic reaction.

1.1 Industrial Example

The asymmetric catalytic hydrogenation of S-enamide is a very important and frequently encountered type of reaction in the production of pharmaceuticals. Specifically, during the first development steps it has been demonstrated that the

desired (R,S) product could not be selectively obtained out of the four stereoisomers resulting from the hydrogenation step (Singh et al., 2009). Identifying a superior complex catalyst has been the first important step in order to reduce the major products in two. The system on focus here uses such a catalyst and thus consists of only two parallel reactions that are competing for the sites of the catalyst.



The performance of such process is not directly proportional to the addition of catalyst, which is custom made and very expensive. In addition, the reaction system is sensitive to the selection of the proper conditions that favor the maximum yield towards the desired product (Blackmond, 2000).

1.2 Process Performance

This process needs to be optimized by maximizing the yield and directing the selectivity of the reaction towards the desired product, optimizing a process response.

The main process responses for the hydrogenation process are: yield towards the desired product (Y), diastereoselectivity (de), and the economic performance index (PI).

Diastereoselectivity is calculated by Eq. 1.3 and the other response, Y , is accounted in the PI, Eq. 1.4.

$$de = \frac{C_{(1R,4S)} - C_{(1S,4S)}}{C_{(1R,4S)} + C_{(1S,4S)}} \quad (1.3)$$

The economic performance index describes the process performance using industrial cost data, and it is subject to constraints derived from product quality specifications.

$$PI = [\alpha_1 C_{(1R,4S)} - \alpha_2 C_{Enamide} - \alpha_3 C_{Norphos}] * V - \alpha_4 t_b \quad (1.4)$$

subject to: $de > 95\%$

where: $C_{(1R,4S)} (kg/l) = Y C_{Enamide} (kg/l)$, and

$\alpha_1 =$ product price (\$/kg), $\alpha_2 =$ reactant cost (\$/kg)

$\alpha_3 =$ catalyst cost (\$/kg), $\alpha_4 =$ labor/energy cost (\$/kg)

This index needs to be maximized with respect to the reaction conditions; such as temperature, catalyst loading, excess of the reactant relative to its solubility at the initial conditions, and batch time.

The optimization first involves the development of an appropriate response surface model for the yield to the desired product, Y , and de . After substituting these to Eq. 1.4, we find the operating conditions that maximize the economic performance index, while the diastereoselectivity is kept above a specific bound, through constrained optimization (Edgar, 2001). Sequential Quadratic Programming (SQP) is then utilized to solve the constrained problem.

2. EXPERIMENTAL PART

In order to acquire the required data for the optimization, we perform statistically designed experiments using state of the art equipment, at the facilities of Sepracor, Inc. The hydrogen uptake is monitored online and sampling is performed at the end of the reaction.

2.1 Equipment and Experimental Setup

The experiments are performed initially in the ChemSCAN, a small scale reactor system with 8 parallel reactors of 20mL each, and then in a larger scale reactor vessel of 1000mL in the Büchi autoclave controlled by the Büchi gas press-flow controller, (BPC). The main advantages of the high pressure ChemSCAN reactor are: 1) the high throughput capability to test several conditions, 2) the small volume that allows screening even if small quantities of material are available, and 3) the online monitoring of hydrogen uptake. However, the magnetic agitator prevents ideal mixing, and possibly introduces mass transfer limitations in the system. The 1000ml hastelloy reactor operated in the Büchi autoclave coupled with BPC, resolves the problems that appear when ChemSCAN is used. In the Büchi system, we achieve precise pressure control, exact measurement of the headspace and ideal mixing, using a gas shaft agitator and a baffle. The jacket temperature for both reactors is controlled by the Lauda Proline RP 845C chiller. The chiller has the capability to run time evolving temperature profiles, which is needed in the case of the DoDE runs and to apply feedback temperature control, attaching an external Pt100 probe that controls the reactor temperature instead of the jacket temperature. Finally,

the reactor temperature is monitored and logged during the reaction by the automation tool of HEL, ChemLog.

2.3 Sampling and Analytical Data

During the reaction, the hydrogen uptake is monitored online using the BLS2 software, developed for use with the Büchi hydrogenation equipment. BLS2 handles data recording, control functions, data export and is used to control the BPC.

The end of the reaction is defined as the point where the hydrogen uptake reaches a plateau. The sampling is done at the end of each reaction. HPLC analysis of the samples results the concentration of the reaction mixture at the end and enables the calculation of the yield and the de .

3. METHODOLOGY

Classical factorial design of experiments has been used initially to identify the factors that significantly affect the system. Then, D-Optimal DoE and D-Optimal DoDE have been used to design experiments. The experimental results have been used to develop response surface models. Optimization has been performed using the two models.

3.1 Classical Design of Experiments (DoE)

The classical Design of Experiments (DoE) approach entails: 1) the selection of the factors that significantly affect the process, 2) the definition of the operating window for each factor, and 3) the selection of the experimental design, out of numerous choices available like: full or half factorial, D-optimal, Plackett-Burnham, Taguchi, central composite and others developed according to the needs of specific types of problems (Montgomery, 2005).

For example, for the asymmetric catalytic hydrogenation case, the significant process factors initially are temperature, pressure, and catalyst loading. A preliminary 3-factor 2-level factorial design provides us valuable information regarding the effect of those variables on the responses of interest.

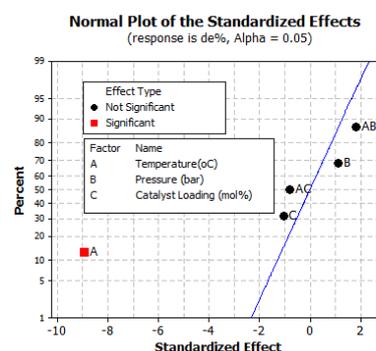


Fig. 1. Normal Probability Plot of the effects on de .

The Analysis of Variance (ANOVA) of the preliminary experiments provides the guidelines for further process optimization. From the ANOVA of the de (Fig. 1), it is obvious that the temperature is the factor with the most significant effect on the process (Burnham and Anderson, 1998; Dillon and Goldstein, 1984). Thus, this is the variable that we should examine in greater detail into the next phase of experimental design. At the same time, ANOVA of the

yield, Y , response surface also shows that temperature is the most important variable and the next most important is the catalyst loading and it should be kept as a design factor. Pressure does not affect the de, and it is less important for the yield, so it will be omitted in the next design loop. Thus, the second phase of DoE experiments will include 2 out of the 3 factors of the preliminary design, plus two more factors important for the final process development: the initial excess of the reactant and the batch time.

Keeping in mind that we seek to eventually optimize the process using a response surface model, we need a response surface design to plan the experiments. The most common response surface design is the central composite design, CCD. In order to fit a four factor full quadratic model it would require 28-30 runs, depending on the number of center points. Because each run is expensive and time consuming, we select a D-Optimal experimental design instead, that results in the minimum number of runs in order to fit a four factor quadratic model. The D-optimal design minimizes the volume of the joint confidence region of the vector of regression coefficients.

The formula that expresses the volume is:

$$V = |(X'X)^{-1}| \quad (3.1)$$

where X : the design matrix. A measure of relative efficiency, D_e , is used in order to compare the D-optimal design, X_2 , with the CCD, X_1 , when a p parameters response surface model is considered.

$$D_e = \left(\frac{|(X_2'X_2)^{-1}|}{|(X_1'X_1)^{-1}|} \right)^{1/p} \quad (3.2)$$

Table 1. 4-Factor D-Optimal DoE

Run	x_1 (T)	x_2 (RE)	x_3 (CL)	x_4 (BT)
1	-1	0	1	-1
2	1	-1	1	1
3	-1	-1	-1	-1
4	-1	1.67	1	1
5	1	-1	1	-1
6	-1	-1	-1	1
7	-1	-1	1	0
8	-1	1.67	-1	0
9	1	1.67	-1	1
10	1	1.67	-1	-1
11	-1	1.67	0	-1
12	1	1.67	1	0
13	0	1.67	1	-1
14	1	-1	-1	0
15	0	0	0	0
16	0	0	0	0
17	0	0	0	0

In Table 1, the coded values of the factors are given. The corresponding uncoded intervals for each factor are: 1)

temperature, $T \in [20^\circ\text{C}, 45^\circ\text{C}]$, 2) catalyst loading, $CL \in [0.03\text{mol}\%, 0.09\text{mol}\%]$, 3) reactant excess, $RE \in [0\%, 500\%]$, and 4) batch time, $BT \in [2\text{h}, 4\text{h}]$.

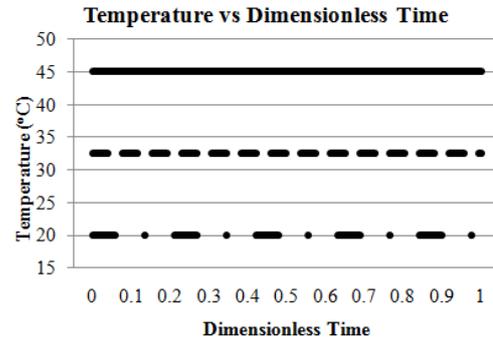


Fig. 2. Temperature levels for D-Optimal DoE.

Fig. 2 illustrates the three time-invariant (constant with time) trajectories that the temperature follows during the runs of the D-Optimal DoEs. The common characteristic of all the classical experimental design techniques is that the value of each decision variable is kept constant during the experiment. This characteristic is the main difference between the classical DoE and the new DoDE approach.

3.2 Design of Dynamic Experiments (DoDE)

The Design of Dynamic Experiments (DoDE) is a systematic approach in designing experiments in which some factors will be varied with time in order to discover optimal operating condition in a equally expedient manner as in the classical DoE approach (Georgakis, 2008, 2009). The DoDE approach replaces the static value of some factor with a time dependant profile characterized by a linear combination of some basis time functions, appropriately selected.

Besides the issues that are important in the DoE design, the DoDE design entails the choice of the factor(s) whose variation with time will be considered and the selection of the basis functions to describe time dependence along with the maximum number of such functions to be used.

In applying the DoDE approach in the case of the asymmetric catalytic hydrogenation, we include all the factors of the classical DoE design described in the previous section, namely: temperature, catalyst loading, initial amount of the reactant and batch time.

According to the ANOVA analysis of the preliminary design, temperature has been identified to have a significant effect on the process outcome. Consequently, this will be the one whose time dependency will be examined. The orthogonal basis function that will be used is the Shifted Legendre Polynomials (Abramowitz and Stegun, 1970). Here we will consider only the first two shifted Legendre polynomials as they will serve our goal to operate our process under linearly changing temperature profiles.

$$P(\tau) = \alpha_0 P_0(\tau) + \alpha_1 P_1(\tau) \quad (3.3)$$

$$P_0(\tau) = 1 \text{ and } P_1(\tau) = 2\tau - 1 \quad (3.4)$$

Because of the two orthogonal polynomials used, the initially four factors become five, with two describing the temperature vs. time profile. In the DoDE as well in the DoE designs the independent variables (factors) are defined in terms of the coded (dimensionless) variables that are between $[-1,1]$. There is an exception here on the x_4 factor, where the maximum value is 1.67, instead of 1.

Because, the temperature profile is subject to the constraint $-1 \leq P(\tau) \leq +1$ this requires that:

$$-1 \leq \alpha_0 \pm \alpha_1 \leq +1 \quad (3.5)$$

The values of the coefficients a_0 and a_1 are the two factors (or dynamic sub-factors) describing the temperature profile. They can individually take the values of -1, 0 and +1 as all other factors and they have also to satisfy eq. (3.5).

The set of experiments is defined in coded variables using the rowexch function of the Matlab Statistics toolbox and it is presented in Table 2.

Table 2. Constrained 5-Factor D-Optimal DoDE in coded variables.

Run	x_1 (a_0)	x_2 (a_1)	x_3 (RE)	x_4 (CL)	x_5 (BT)
1	-0.5	0.5	-1.0	1.0	-1.0
2	0.5	0.5	-1.0	1.0	1.0
3	-0.5	0.5	1.67	1.0	1.0
4	0.5	0.5	-1.0	-1.0	-1.0
5	0.5	-0.5	-1.0	-1.0	1.0
6	0.5	-0.5	1.67	-1.0	-1.0
7	1.0	0.0	0.0	-1.0	1.0
8	0.5	0.5	1.67	0.0	0.0
9	0.0	-1.0	1.67	-1.0	1.0
10	0.0	-1.0	0.0	1.0	0.0
11	-0.5	0.5	1.67	-1.0	-1.0
12	0.5	-0.5	1.67	1.0	1.0
13	-0.5	-0.5	-1.0	-1.0	-1.0
14	-0.5	0.5	-1.0	-1.0	1.0
15	-0.5	-0.5	-1.0	1.0	-1.0
16	1.0	0.0	-1.0	1.0	-1.0
17	0.0	0.0	1.67	0.0	-1.0
18	0.5	0.5	1.67	1.0	-1.0
19	-0.5	-0.5	1.67	1.0	0.0
20	-1.0	0.0	-1.0	1.0	1.0
21	-0.5	-0.5	0.0	0.0	1.0
22	0.0	0.0	0.0	0.0	0.0
23	0.0	0.0	0.0	0.0	0.0
24	0.0	0.0	0.0	0.0	0.0

The corresponding uncoded intervals for each factor are: for 1) temperature, $T \in [20^\circ\text{C}, 45^\circ\text{C}]$, 2) catalyst loading, $\text{CL} \in [0.03\text{mol}\%, 0.09\text{mol}\%]$, 3) reactant excess, $\text{RE} \in [0\%, 500\%]$, and 4) batch time, $\text{BT} \in [2\text{h}, 4\text{h}]$.

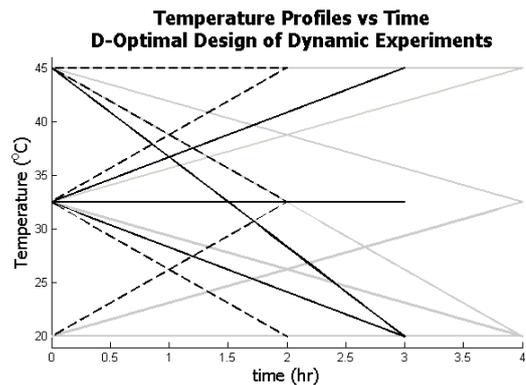


Fig. 3. Temperature levels for the 5-Factor D-Optimal DoDE

In Fig. 3, the temperature profiles are presented for the three time horizons of the D-Optimal design. These profiles result by substituting the design coefficients in Eq. 3.5 for each run and transferring dimensionless time, τ , into the dimensional one, t , through the batch time.

The procedure of the temperature profiles construction is presented in Table 3. The linear combination of the design coefficients (columns 1 & 2) lies in column 3 and the translation of the profiles in uncoded variables in column 4. For $\tau=0$, we get the initial temperature for the reaction and for $\tau=1$ the final one.

Table 3. DoDE Temperature profiles construction.

Run	x_1 (a_0)	x_2 (a_1)	$P(\tau)$	$T(t)$ ($^\circ\text{C}$)
1	-0.5	0.5	$-0.5+0.5(2\tau-1)$	$20 \rightarrow 32.5$
2	0.5	0.5	$0.5+0.5(2\tau-1)$	$32.5 \rightarrow 45$
3	-0.5	0.5	$-0.5+0.5(2\tau-1)$	$20 \rightarrow 32.5$
4	0.5	0.5	$0.5+0.5(2\tau-1)$	$32.5 \rightarrow 45$
5	0.5	-0.5	$0.5-0.5(2\tau-1)$	$45 \rightarrow 32.5$
6	0.5	-0.5	$0.5-0.5(2\tau-1)$	$45 \rightarrow 32.5$
7	1.0	0.0	$1.0+0.0(2\tau-1)$	45
8	0.5	0.5	$0.5+0.5(2\tau-1)$	$32.5 \rightarrow 45$
9	0.0	-1.0	$0.0-1.0(2\tau-1)$	$45 \rightarrow 20$
10	0.0	-1.0	$0.0-1.0(2\tau-1)$	$45 \rightarrow 20$
11	-0.5	0.5	$-0.5+0.5(2\tau-1)$	$20 \rightarrow 32.5$
12	0.5	-0.5	$0.5-0.5(2\tau-1)$	$45 \rightarrow 32.5$
13	-0.5	-0.5	$-0.5-0.5(2\tau-1)$	$32.5 \rightarrow 20$
14	-0.5	0.5	$-0.5+0.5(2\tau-1)$	$20 \rightarrow 32.5$
15	-0.5	-0.5	$-0.5-0.5(2\tau-1)$	$32.5 \rightarrow 20$
16	1.0	0.0	$1.0-0.0(2\tau-1)$	45
17	0.0	0.0	$0.0-0.0(2\tau-1)$	32.5
18	0.5	0.5	$0.5+0.5(2\tau-1)$	$32.5 \rightarrow 45$
19	-0.5	-0.5	$-0.5-0.5(2\tau-1)$	$32.5 \rightarrow 20$
20	-1.0	0.0	$-1.0-0.0(2\tau-1)$	20
21	-0.5	-0.5	$-0.5-0.5(2\tau-1)$	$32.5 \rightarrow 20$
22	0.0	0.0	$0.0-0.0(2\tau-1)$	32.5
23	0.0	0.0	$0.0-0.0(2\tau-1)$	32.5
24	0.0	0.0	$0.0-0.0(2\tau-1)$	32.5

3.3 Response Surface Model Technique Review (RSM)

The Response Surface Method (RSM) is used to quantify the dependence of yield towards the desired product, Y, and the diastereoselectivity, de, on the experimental factors (Box and Draper, 2007; Montgomery, 2005). The response surface model has a polynomial form as it represents a local Taylor series approximation of the true dependence on the input factors. Here we estimate quadratic models.

The RSM model for Y is used to calculate the dependence of the economic performance index, PI, on the experimental conditions. Constrained optimization seeks to calculate the conditions that maximize the performance index, PI, while the value of the diastereoselectivity, de, is higher than the value of the product quality required like 0.95, 0.96 or higher. The optimum values of the two first factors, a_0 and a_1 , relate to the optimal temperature profile for the process of asymmetric catalytic hydrogenation examined here.

4. EXPERIMENTAL RESULTS

After running the experimental designs presented in Tables 1 & 3, and performing the HPLC analysis of the samples we are able to calculate the yield, the de (Eq. 1.3) and the PI (Eq. 1.4) for each run.

The PI is initially used to rank the desirability of the sets of conditions tested in the two designs. Summarizing the results we get the following table:

Table 4. The best PIs, de and Y for DoE and DoDE experiments.

	PI (\$/l)	de (%)	Yield (%)	T (°C)	CL (mol%)	RE (%)	BT (hr)
Best Initial DoE Run	726	96.8	95.4	20.0	0.03	500	3
Best Initial DoDE Run	1076	94.6	96.2	45→ 32.5	0.06	500	1.0
Center Point	500	95.5	97.3	32.5	0.06	250	0.7

The best DoDE run, closest to 95% de specification, appears a PI 45% better than the one of the best DoE run and this is a significant improvement in the process. This was achieved by performing 24 vs. 17 experiments for the DoDE and DoE designs respectively.

The improvement is mainly achieved because the volumetric productivity of the process is increased for the best DoDE run. The reactant excess is for both runs at the same relative level, but because it is a function of solubility, the initial temperature is the factor that defines how much reactant could be loaded in each batch. Thus, the volumetric productivity is higher the higher the initial temperature is, but the final diastereoselectivity decreases the higher the temperature the reaction runs at. The decreasing temperature profile in the DoDE benefits the process in the fashion that it allows the maximization of volumetric productivity keeping product quality close to specification.

5. RSM MODELING AND OPTIMIZATION

The economic performance index is the main response that will be optimized, while the de is the secondary response that is required to be above 95%. The response surface of the secondary response, de, is developed and used as a non-linear constraint during the SQP optimization of the PI. The regression coefficients for the two RSM's are calculated utilizing the design matrices as the regressors and the measured values of the Y and de as responses. In some of the runs the real reaction completes at an earlier time than the designed batch time, judging by the online monitoring of the hydrogen uptake. Thus, the initially planned batch time, BT, for some experiments needs is reduced to a value that corresponds to the actual reaction time. Consequently, the DoDE coefficients a_0 and a_1 are re-calculated.

5.1 DoE Response Surface

The full quadratic response surface model for the DoE design of 4 factors, involves 15 terms. These include the constant term, the 4 linear terms of the respective decision variables, the 6 second order interactions between factors and the 4 quadratic terms. The ANOVA of the full model reveals which of the terms are significant (p-value<0.05). Insignificant terms are removed, to obtain the final model.

$$Y_{DoE} = \beta_0 + \beta_1x_1 + \beta_2x_2 + \beta_{12}x_1x_2 + \beta_{13}x_1x_3 + \beta_{14}x_1x_4 + \beta_{11}x_1^2 \quad (5.1)$$

A model with only 7 terms, instead of the initial 15, is sufficient to accurately describe the process, eq. 5.1. The model is quite accurate, as demonstrated by the following statistical criteria: $R^2=95.9\%$, $R^2_{adj}=92.7\%$, and $PRESS=0.15$. For the de response surface, a 7 terms model describes the surface with: $R^2=98.1\%$, $R^2_{adj}=96.9\%$, and $PRESS=6.64$.

$$de_{DoE} = \beta_0 + \beta_1x_1 + \beta_2x_2 + \beta_{13}x_1x_3 + \beta_{23}x_2x_3 + \beta_{24}x_2x_4 + \beta_{33}x_3^2 \quad (5.2)$$

5.2 DoDE Response Surface

The full quadratic response surface model for the DoDE set of experiments involving five factors consists of 21 terms. These include the constant term, the 5 linear, the 10 second order and the 5 quadratic terms. The ANOVA step with p-value<0.05 retains only the following 8 terms:

$$Y_{DoDE} = \beta_0 + \beta_3x_3 + \beta_{12}x_1x_2 + \beta_{24}x_2x_5 + \beta_{34}x_3x_4 + \beta_{45}x_4x_5 + \beta_{22}x_4^2 \quad (5.3)$$

Here the model is less accurate because of the asymmetrical enlargement of the design space caused by experiments that run faster than expected and result in shorter batch times. In this case, $R^2=84.6\%$, $R^2_{adj}=77.9\%$, and $PRESS=0.76$. For the de% response surface, a 6 terms model is sufficient with: $R^2=89.5\%$, $R^2_{adj}=86.6\%$, and $PRESS=8.44$.

$$de_{DoDE} = \beta_0 + \beta_1x_1 + \beta_{25}x_2x_5 + \beta_{35}x_3x_5 + \beta_{11}x_1^2 + \beta_{44}x_4^2 \quad (5.4)$$

5.3 Constrained Optimization

The constrained optimization problem is solved using the SQP algorithm of the Optimization Toolbox of Matlab R2008b that utilizes the Quasi Newton approach and line search method in order to reach the optimum (Biegler, 1984). The optimization has been run for different final product quality ($de > 0.95$, 0.96 or 0.97) and the medium quality optimum ($de > 0.96$) is given in Table 5.

The constraints involve upper and lower bound for each of the decision variables and the eq. 3.6 constraints. The latter uses the response surface model developed for the de , which depends nonlinearly on the decision variables.

Table 5. Optimization results and optimum runs.

	T (°C)	CL (mol %)	RE (%)	BT (hr)	de (%)	Yield (%)	PI (\$/l)
Opt. DoE & CI	22	0.06	500	1.4	96.5 ±0.5	94.3 ±9.3	1061.9 ± 18.9
Exp DoE	22	0.06	500	1.4	96.9	83.3	567.2
Opt. DoDE & CI	45→20	0.08	500	3	96.4 ±0.4	99.0 ±17.3	1386.1 ± 37.8
Exp DoDE	45→20	0.08	500	3	96.2	92.6	1223.4

The calculated optimal DoDE run for a medium quality involves a decreasing temperature profile and predicts a 30.5% improvement in the process than the optimal DoE run. This is a significant improvement in the process with just seven additional experiments. Performing the experiments in the optimal conditions shows an even larger improvement is achieved, as indicated in Table 5, where $PI_{DoDE,exp}=1223.4$ \$/l and $PI_{DoE,exp}=567.2$ \$/l. However, this partially happens because the designed batch time is not sufficient for the reactions to reach completion. Thus, the need for feedback control and an online monitoring technique appears. The hydrogen uptake monitoring serves this purpose in this case, and after we sample, we let the reactions run until completion; the DoE for 0.4hr more and the DoDE for 0.1hr more. After the completion of the reactions, the DoDE run shows a 68.1% higher PI comparing to the respective DoE one; with $Y_{DoDE,exp_final}=95.2\%$, $PI_{DoDE,exp_final}=1290.4$ (\$/l), and $Y_{DoE,exp_final}=97.7\%$, $PI_{DoE,exp_final}=767.5$ (\$/l).

The decreasing temperature profile results in an increase of the solubility of the reactant initially, while it preserves the high quality of the product at the end. This provides the option of loading a higher amount of reactant in the reactor in the beginning, and leads to increased volumetric productivity. At the same time, due to the sensitivity of the product quality, which is lower at high temperatures (unacceptable quality results if the reaction is run at a constant temperature above 39°C) and high at the low end of the temperature range, the process proves so much more valuable. Even though it enables reaction to start at a higher temperature, most of the course of the reaction is completed at the part of the range that provides high quality product.

6. CONCLUSIONS

The pharmaceutical reaction of asymmetric catalytic hydrogenation has been investigated in this research work. We have compared the classical DoE and the novel DoDE design the experiments methodologies. The DoDE approach examines new optimization possibilities and enables further process optimization in new trajectories that cannot be studied with the DoE approach. The optimal DoDE run that involves a decreasing temperature profile for a medium quality product predicts 30.5% improvement over the best optimal DoE run. The RSM predicts larger differences the better the quality of the final product required. This difference is even larger if the experiments that the optimum predicts are run, reaching 68.1%. The decreasing temperature profile results in an increase of the solubility of the reactant initially that enhances volumetric productivity, faster reaction and high quality end product. Concluding the DoDE approach is a significant contribution towards the data-driven rapid optimization of batch reactions using an RSM model.

REFERENCES

- Abramowitz, M., and I. A. Stegun, 1970, Handbook of Mathematical Functions: New York, Dover Publication Inc.
- Biegler, L. T., 1984, Solution of dynamic optimization problems by successive quadratic programming and orthogonal collocation: Computers & Chemical Engineering, Volume 8, p. 243-247.
- Blackmond, D. G., 2000, Kinetic aspects of nonlinear effects in asymmetric catalysis: Accounts of Chemical Research, v. 33, p. 402-411.
- Box, G., and N. Draper, 2007, Response Surfaces, Mixtures and Ridge Analysis: Hoboken, NJ, John Wiley & Sons.
- Burnham, K. P., and D. R. Anderson, 1998, Model Selection and Multimodel Inference.
- Dillon, W. R., and M. Goldstein, 1984, Multivariate Analysis: Methods and Applications, John Wiley and Sons.
- Edgar, H., Lasdon, 2001, Optimization of Chemical Processes: Chemical Engineering Series: New York, McGraw Hill.
- Espie, D., and S. Macchietto, 1989, The Optimal-Design of Dynamic Experiments: AIChE Journal, v. 35, p. 223-229.
- Georgakis, C., 2008, Dynamic Design of Experiments for the Modeling and Optimization of Batch Process.
- Georgakis, C., 2009, A Model-Free Methodology for the Optimization of Batch Processes: Design of Dynamic Experiments, ADCHEM, Istanbul.
- Montgomery, D. C., 2005, Design and Analysis of Experiments, John Wiley & Sons, Inc.
- Pisano, G. P., 1996, Learning-before-doing in the development of new process technology: Research Policy, v. 25, p. 1097-1119.
- Pisano, G. P., 1997, The Development Factory: Lessons from Pharmaceuticals and Biotechnology, v. Research Policy 25: Boston, Harvard Business School Press.
- Singh, S. P., S. G. Koenig, and T. R. Wagler, 2009, Catalytic asymmetric hydrogenation of enamides Problems and challenges on scale: Chimica Oggi-Chemistry Today, v. 27, p. 23-25.