

Articles

An Integrated Approach Combining Reaction Engineering and Design of Experiments for Optimizing Reactions

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Abstract:

A certain number of reactions in the organic synthesis pose serious scale-up problems; on the other hand, other reactions create safety issues that must be addressed early during process development. The following work shows a statistical analysis of different reactions in terms of kinetics and phases (solid–liquid–gas). It also introduces an approach that permits a rapid identification of these sensitive reactions so that a better allocation of resources can be performed from the start of a project.

Introduction

Many tools are available for a process R&D chemist to perform an optimization of a synthetic route designed for production. By mentioning some of them—design of experiments (DOE), use of laboratory automates, on-line monitoring of reactions, simulation tools—are all appropriate and valuable tools. Some of these tools might require a specialized person/team (internal) or even an external consultant to be applied properly. In such cases the amount of resources attributed to a project might increase considerably. The prime question is: how can one optimize the allocation of resources to projects and work with the different tools properly from the start of a project?

The following work introduces an R&D methodology that was elaborated to address such problems. It will also give an overview of the different types of reactions that are present in the fine chemical/pharmaceutical sector based on Lonza's experience within the last 2 years. The reactions will be subdivided in three classes: semi-batch (rapid), semi-batch (moderate), and batch (slow). This classification will be the starting point of a reaction-engineering analysis and will set the basis of design of experiments.

Importance of Reaction Engineering

A multipurpose plant is usually based on a train/stream approach where a solid key reagent from a previous step is introduced and a crystalline product is obtained.¹ Product isolation is a fundamental requirement of such installations and entails unit operations such as liquid–liquid extraction, distillation, crystallization, washing, and filtration. To optimize the number of downstream unit operations, multistep

Table 1. Averages characteristic of 22 different processes which refer to production campaigns where a solid intermediate or final product is obtained (mainly pharmaceutical)

average yield [%]	unit operations reaction	unit operations workup
77	2.1	2.7

syntheses are favored as long as the product quality remains acceptable. Table 1 shows the number of reaction steps in comparison to the number of downstream operations of 22 different processes in production at Lonza.

The amount of workup and downstream operations is comparable to the number of chemical steps (even slightly higher). However, it is important to point out that downstream operations are a direct consequence of the reaction steps. For example an increase of 10% yield during a reaction means fewer side products and usually a less demanding workup procedure. Moreover, the reasonable average yield per campaign (77%) indicates that a further optimization potential remains during production. For the sake of clarity, we will limit this paper to the analysis of reaction-engineering aspects only. Nevertheless, for a complete process optimization both types of unit operations must be considered as a whole.

The Approach/Methodology

Laboratory automate reactors can be separated into two classes. Some apparatus such as the RC-1 (Mettler Toledo) give much information in a single experiment. Other apparatus, such as the Flexylab (Systag), ReactArray (Anachem), and Radleys Carousel (Radleys), are very useful to conduct parallel experiments.

The Lonza approach is to use the reaction calorimeter (RC-1) as an integrated method in process development. This tool is not used exclusively in the safety and hazard department. When a process is transferred from a pharmaceutical company to Lonza, it is very useful to perform the initial “familiarization” reactions with a RC-1. Basic information is acquired that will influence the whole process development. An ideal process development strategy is presented in Table 2. The basic idea of this approach has already been described in the literature² and in a textbook.³ However, we emphasize here the importance of performing

(1) Ainsworth, D.; Brocklebank, M. *Chem. Eng.* 2003, July, 42–49.

Table 2. Ideal process development strategy

I	early phase RC-1 (to get as much information as possible)
II	familiarization experiments with laboratory automates (optional)
III	design of experiments → screening (for example with ReactArray)
IV	design of experiments → optimization (for example with Flexilab)
V	RC-1
VI	pilot production or large-scale production

an early phase RC-1 before starting a DOE to obtain a basic understanding of a process in terms of:

- Enthalpy
- Kinetics
- Mass balance
- Type of phases

This RC-1 evaluation belongs, in a certain sense, to the familiarization reactions at the beginning of a process development. Indeed, we would suggest to carry on with a DOE when the chemical knowledge permits an anticipation of a linear influence of the different factors. A screening DOE which determines and weighs the effect of main factors and interactions assumes that the system is linear. This is a fundamental initial assumption that is sometimes difficult to fulfill at the beginning. A typical example is the influence of solvents. The reactivity might be entirely different in one solvent, or its effect might be so dominant that it hides completely the other factors. Such nonlinear or black and white effects at the beginning of process development must not be underestimated. Useful experiments are to perform two runs, one with all factors high and the other with all factors low. As a matter of fact, experience and chemical intuition play a most critical role at that stage.

Nevertheless, if a chemist chooses to run the reactions in the traditional manner (one factor at a time) one must gain as much information as possible in one single run. In such situations it is not economical to continue working in the RC-1, and a high level of laboratory automation is required. Indeed, a lot of information found with the RC-1 can be obtained in a qualitative manner with less expensive laboratory automates such as the LabMax (Mettler Toledo), Syntalab, and Midilab (both Systag). Parallel laboratory automates (Flexilab, ReactArray, etc.) are also useful here to speed up development. In our case, any chemist who wishes to upgrade his laboratory to a modern facility can receive or work with such an automate.

Reaction Overview. When running a reaction in the RC-1, the enthalpy of reaction can be measured quite precisely. This enthalpy is usually a mix between heat of mixing and heat of reaction. If we assume that heat of mixing does not play a significant role (this is not always true), the experimental enthalpy can be compared to the theoretical value that is expected for the type of reaction under study.⁴ A significant difference between both values might suggest

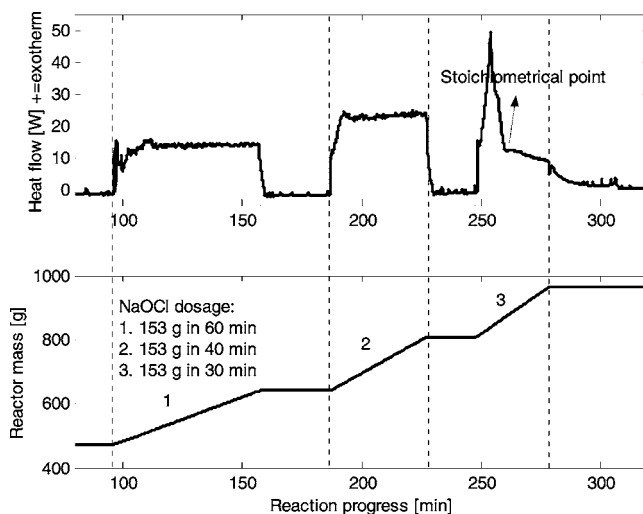


Figure 1. Example of a class I reaction where a C=C double bond is oxidatively cleaved by aqueous NaOCl catalyzed by Ru.⁵ The reaction is rapid and proceeds without accumulation ($T = 5\text{ }^{\circ}\text{C}$) although the starting reagent is a solid with a low solubility (0.8 wt %).

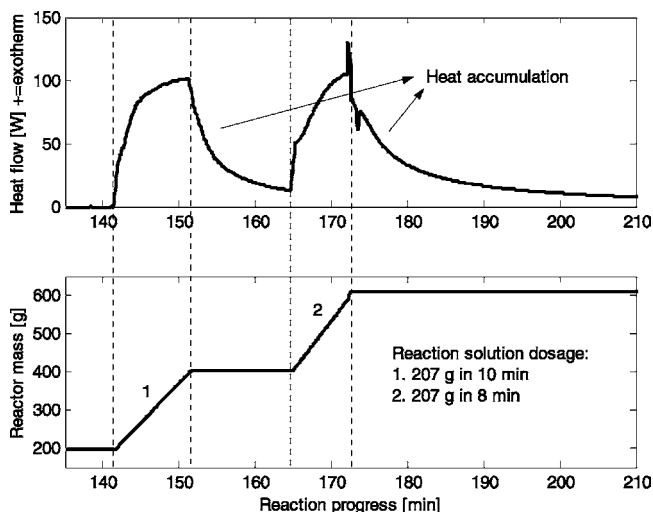


Figure 2. Example of a class II reaction where a solution treated with ozone is quenched into a methanol/dimethyl sulphide solution. The temperature ($T = 25\text{ }^{\circ}\text{C}$) is critical in such a way that lower temperatures favor high accumulation of heat and higher temperatures favor formation of side products.

that the reaction is not completed or that major side reactions are taking place.

Overview in Terms of Kinetics. The main advantage of using a RC-1, however, is to obtain information about reaction kinetics. With the help of RC-1, reactions can be classified in one of the following classes:

I. Semi-batch reactions with no accumulation of energy (rapid reactions, Figure 1).

II. Semi-batch reactions with accumulation of energy (moderate reactions, Figure 2).

III. Batch reactions or semi-batch reactions with more than 70% accumulation of energy (slow reactions, Figure 3).

Class I reactions show no heat accumulation, i.e., the heat signal is a function of the dosage speed and reduces to zero when dosage is interrupted (Figure 1). This definition is, of course, a function of the dynamic response of the calorimeter.

(2) Owen, M. R.; Luscombe, C.; Lai, L.-W.; Godbert, S.; Crookes, D. L.; Emiataba-Smith, D. *Org. Process Res. Dev.* **2001**, *5*, 308–323.

(3) Erikson, L.; Johansson, E.; Kettaneh-Wold, N.; Wikström, C.; Wold, S. *Design of Experiments. Principles and applications*; Umetrics: Umea, 2000.

(4) Bender, H.; Müller, M.; Conrad, D.; Walther, C.-D.; Berthold, W.; Glor, M.; Wandrey, P.-A.; Mix, K.-H.; Steinbach, J.; Eberz, A.; Stoessel, F. In *Ullmann's Encyclopedia of Industrial Chemistry*; Wiley-VCH: Online article, 2000.

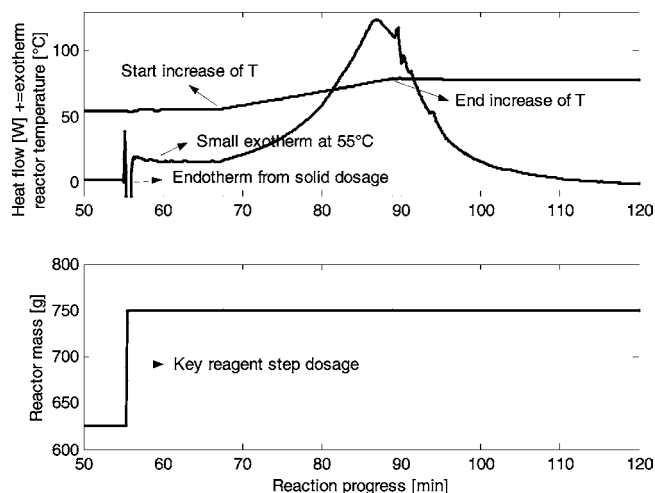


Figure 3. Example of a class III reaction in which an intramolecular aromatic ring condensation takes place (Knoevenagel-type reaction catalysed by NaOH). A key reagent is dosed at 55 °C, and the reaction is started by heating the reaction mixture to 75 °C.

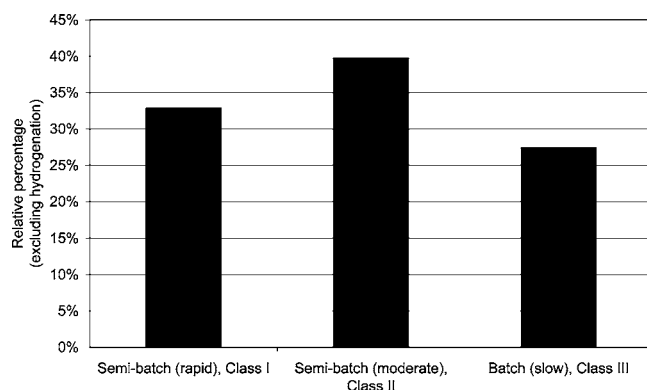


Figure 4. Analysis of 86 different reactions which were characterized in the RC-1 prior to being transferred into pilot- or large-scale production. The reactions are classified in one of the defined classes.

From experience, we assume with the RC-1 that a reaction completed in less than 3 min shows no accumulation (within the typical laboratory dosage rate, see Figures 1–3).

Class II reactions show heat accumulation, i.e., not only does the heat signal depend on the dosage rate, but also a certain amount of reagent accumulates and reacts after the end of the dosage (Figure 2).

Class III reactions exhibit high accumulation of energy, i.e. most of the heat potential evolves after the dosage of reagents (accumulation higher than 70%) or the reaction is run batch-wise (Figure 3). A batch reaction can be started by increasing the reaction temperature or introducing a catalyst. Autocatalytic reactions, where an induction period is observed before the start of reaction, would also be sorted into class III.

Figure 4 shows the analysis of 86 different reactions that were characterized in the RC-1 prior to a technical transfer into pilot (or large-scale) production. It is interesting to note that more than 70% of all reactions are run in a semi-batch modus (classes I and II together). Indeed, this modus permits a very good reaction control and ensures that the reaction can be safely scaled up provided only a low accumulation

occurs. In case of unexpected behavior the dosage is simply interrupted.

Each reaction class has different fundamental attributes that must be addressed in a different manner. Class I reactions have the potential to be very sensitive to scale-up. Typical relaxation times for micromixing are in the range of less than 1 s.⁶ If we recall that class I reactions are completed in less than 3 min, there is a high potential for them to lie in the mixing controlled domain. For such an analysis (Figure 1), it is important not to use the end accumulation as an indication of the reaction kinetics. At that point (close to stoichiometry) side reactions might play a dominant role related to a different mechanism.

On the other hand, class III reactions accumulate most of the heat potential; they might create safety issues during scale-up that must be addressed early during process development. In such a case, dynamic simulations might be required to investigate different case scenarios to enable safe and efficient processes.⁷ These simulations will only be possible if an appropriate kinetic analysis has been undertaken during the laboratory development. Such analyses are, however, experimentally more demanding than simple DOE modeling.

Within class I and class III reactions, not all the reactions show mixing limitations or safety issues (roughly less than 20% or 10%, respectively, based on all the reactions studied). For example, several batch processes are simply performed at reflux where the reaction heat alone cannot sustain solvent boiling (a need for an external heat source). In such a case, however, an in-process control is required to ensure reaction completion before any further workup stage in order to avoid unexpected accumulations. For the rapid reactions (class I), mixing limitations should be addressed early during process development as, for example, in a screening DOE.

Overview in Terms of Phases (Solid–Liquid–Gas).

The picture becomes more complex when the different reaction phases are taken into account. The importance of this aspect is even often underestimated by the chemist. As shown in Figure 5, less than 25% of all reactions are fully homogeneous, and the majority has to deal with some form of heterogeneity. The most important heterogeneity is the presence of solid phases whether as reagent, catalyst, or product (63%). Reactions involving a gas are important (30%), and hydrogenation (ca. 15%) is the most frequently used single reaction unit operation.

In analogy to the previous analysis, Figure 6 presents the two opposed reaction-engineering scenarios that should be considered during process development. An estimate of the maximum reaction speed (Figure 6 (left)) that could be expected can be evaluated by considering experimental correlations for the different mass transfer coefficients (k_{la} in s^{-1} , k_1 in $(s \cdot m)^{-1}$). Recent reviews of these correlations can be found in the literature.^{8–10} The maximum reaction rate (r in mol/s) that is theoretically possible becomes a

(5) Quittmann, W.; Roberge, D. M.; Bessard, Y. *Org. Process Res. Dev.* **2004**, *8*, 1036–1041.

(6) Bourne, J. R. *Org. Process Res. Dev.* **2003**, *7*, 471–508.

(7) Landau, R. N.; Blackmond, D. G. *Chem. Eng. Prog.* **1994**, November, 43–48.

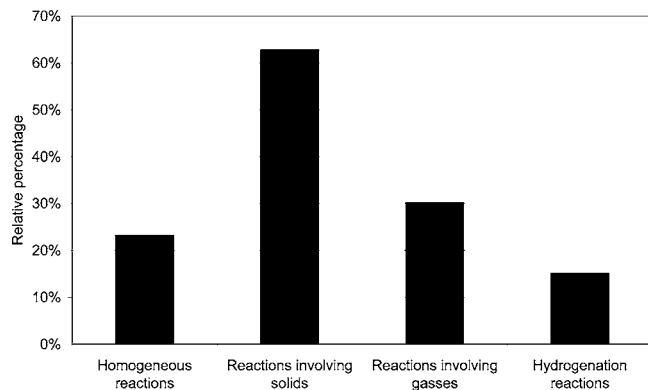


Figure 5. Analysis of 86 different reactions which were characterized in the RC-1 prior to being transferred into pilot- or large-scale production. The reactions are classified in terms of reaction phases (solid–liquid–gas).

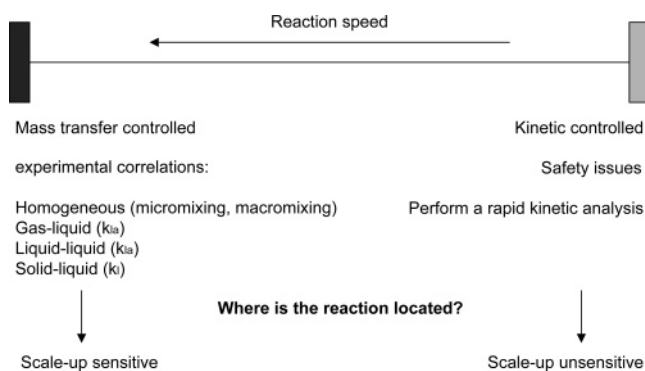


Figure 6. Two opposed reaction engineering scenarios that should be considered during process development.

simple function of the mass-transfer coefficient and the solubility (concentration C in mol/L) of the limiting reagent (approximation, for accurate values the Hatta number must be considered⁶):

$$r = k_{la}CV \quad \text{or} \quad r = k_1aCV$$

(where V = volume in L and a = specific surface area in m^2/m^3).

In comparison to that, the actual reaction rates for class II and class III reactions can be estimated with the RC-1.¹¹ The comparison of both values indicates where the reaction is located on the axis of Figure 6 and gives an idea of the influence of mass-transfer limitations. From experience, however, class II reactions that are mass-transfer limited are relatively rare. For example, Figure 1 shows a solid–liquid reaction where the solubility of the solid reagent in the liquid phase is only 0.8 wt %. Even under such a low solubility, the RC-1 results show typical results for class I reactions. Class II reactions can become mass-transfer limited when the concentration of the limiting reagent is very low. However, this is often true for hydrogenations in organic medium, but this subject should be treated somewhat differently.¹²

The kinetics of class I reactions can vary from a few milliseconds (mixing controlled) up to approximately 3 min. Their exact evaluation requires the use of sophisticated methods such as stopped-flow mixing apparatus.¹³ Nevertheless, three solutions will be mentioned to study the influence of mass-transfer limitations in more detail.

(1) The use of microreactor technology has proven to be a very efficient tool to study micromixing in our laboratory. The contribution of such a technology to process development has already been mentioned in the literature.¹⁴

(2) The use of a small reaction calorimeter with a very fast dynamic response is a direct alternative. A good example is the use of a power compensation calorimeter with integrated Peltier elements eliminating the need for calibration.¹⁵

(3) However, the most pragmatic way to study mass-transfer limitations is to simply integrate the analysis into a screening DOE. These aspects should be integrated into the process R&D and not just when the reaction is mature to be transferred to production.

Design of Experiment. A DOE shall be performed when the chemical knowledge permits an anticipation of a linear influence of the different factors/parameters. As a rule of thumb, this condition is usually satisfied when key parameters such as solvent, type of catalyst, reaction class, and phases are defined. From our point of view the use of a screening DOE is the most efficient way to proceed forward in a project development. A list of arguments to use DOE has been published¹⁶ but we would like to emphasize two major advantages:

- Parameter interactions can be estimated; this is only accessible by the use of a design matrix.
- A rigorous statistical interpretation is obtained which reveals the quality of the experimental data.

Table 3 shows a list of different factors that have potential influence on the reaction. This list is not intended to describe all possible cases. It just emphasizes the need to look at the process differently, depending on the reaction class.

The factors that potentially show a nonlinear trend are the qualitative factors presented in Table 3. These factors are usually fundamental parameters that can strongly influence the chemistry. By inspection of 10 different DOE that were performed recently, three “classic” factors are almost always included in such designs, namely: stoichiometry of reactants, temperature, and concentration (or dilution) of substrates and reagents.

The list of factors for class I reactions is important. All these factors are known to influence to a certain extent the mass-transfer limitations.⁶ A rigorous choice of the appropriate factor has the capability to identify mass-transfer limitations by the use of DOE. On the other hand, for class III

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 (9) Doraiswamy, L. K. *Organic Synthesis Engineering*; Oxford University Press: New York, 2001.
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 (16) Lendrem, D.; Owen, M. R.; Godbert, S. *Org. Process Res. Dev.* **2001**, *5*, 324–327.

Table 3. Potential factors that should be considered in a DOE; the importance of each factor should be weighted as a function of the reaction class

class I	class II	class III
reactant concentration stirrer type stirrer speed dosage position and type particle size (solid–liquid) use of sparger (gas–liquid) amount of catalyst (if applicable) viscosity (uncontrolled)	dosage rate (accumulation) temperature (accumulation) reaction time (aging)	reaction time temperature reaction enthalpy (uncontrolled) product stability (uncontrolled)
classical factors:	proportion (stoichiometry) of reactants reactant concentration or dilution temperature pH (if applicable) dosage sequence	
formulation factors:	solvent proportion (if cosolvent) ratio of phases (organic, aqueous, if applicable) salt concentration	
qualitative factors:	type of solvent type of acid/base type of active reagent (reducing agent, oxidation chemical, etc.) type of catalyst	

reactions the determination of the right reaction time is usually essential. Moreover, an additional concern arises in terms of safety due to the complete heat accumulation. The temperature plays a significant role for class II reactions in such a way that it directly influences the accumulation. Higher temperatures favor less accumulation and cause the reaction to be safely controlled.

The dosage rate is usually not open to much variation in large-scale production. Semi-batch reactions are usually performed at constant temperature, and the maximum cooling capacity determines the dosage time. Details of such calculations can be found elsewhere.¹⁷ Optimal feed-rate policies were also analyzed in depth, but constant dosage speed and isothermal control remain the preferred strategy.¹⁸ Indeed, it is interesting to note that an isothermal strategy combined with a cascade temperature control is a very efficient and probably the most pragmatic method to control the process. Moreover, cascade controls are found in most modern facilities, and in that case, for throughput maximization, the maximum allowed temperature in terms of selectivity should be determined.

A screening DOE determines the most critical factors and sets high/low values for the others. The most straightforward way is to continue in the same direction and perform an optimization with the most critical factors. Here, too, many arguments speak in favor of such a procedure and by mentioning just a few:

- A response surface model is obtained that indicates the true maximum of the process.
- The profile or contour of the maximum is revealed and tells if this maximum is broad or narrow.

(17) Choudhury, S.; Utiger, L.; Riesen, R. Heat transport in agitated vessels: scale-up methods. Mettler Toledo Publication, 00724218, pp 1–15.

(18) Feliu, J. A.; Grau, I.; Alos, M. A.; Macias-Hernandez, J. J. *Chem. Eng. Prog.* **2003**, December, 42–48.

The reaction should now be ready to be transferred to large-scale production. This analysis can be completed with a test for robustness. In addition, after the optimization a safety test using the RC-1 remains imperative; the conditions, kinetics, and enthalpy might have changed from the initial process.

Conclusions

Reaction calorimeters and automated reactors with a design of experiment approach (DOE) should be a central part of process development. To speed up the DOE the use of high throughput automates such as the Flexilab and ReactArray turns out to be imperative. To gain widespread acceptance of DOE, good training and education of chemists is needed. This is also true for reaction engineering aspects such as mass-transfer limitations due to its potential interference in process development (class I reactions).

In contrast, specialists should be strongly involved once a reaction has been found critical in terms of mass transfer limitations or in terms of safety issues. However, such situations, where a specific knowledge is required, remain limited (roughly less than 30% of cases). Empirical modeling, such as a DOE, is a very pragmatic and efficient way to avoid dynamic simulations that are based on a detailed kinetic analysis. Mainly, the critical reactions in term of safety should be addressed in this manner.

A practical example of the application of this approach is presented in ref 5.

Acknowledgment

I thank my colleagues in the Chemical Research and Development department for their support and especially Dr. Colm O' Murchu for his valuable advice during the preparation of this manuscript.

Received for review May 27, 2004.

OP0400160