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Mixed-level supersaturated design application to a robustness study on an organic synthesis

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ABSTRACT

Mixed-level supersaturated designs are designs in which the number of coefficients to estimate is greater than the number of experiments. This type of design is useful in the rapid preliminary investigation of a process with a large number of potentially relevant factors but with only a few of them having important effects. The purpose of this project was to determine the active parameters on a chemical process. A mixed-level supersaturated design of 12 experiments was carried out, allowing us to screen 17 two-level factors and 5 three-level factors. χ^2-optimality of the design was confirmed. In order to verify the results, a 40-run matrix was built. One parameter was identified as very active in both analyses, and several others were suspected to have an effect on the process. Some differences were observed in the results, regarding the detection of the least influent factors. These are likely due to the loss of information generated by the reduction of runs in the supersaturated design, as this kind of design allows an important reduction of the number of experiments. Further studies should be considered to confirm the activity of some factors.

1. Introduction

Screening strategies are effective methods to identify active factors, i.e. influent parameters, in a process, and allow the evaluation of the robustness of a process [1]. They are widely used for the analysis of industrial processes. If the number of factors becomes very large, the number of experiments required by classical screening designs may be impractical, especially if the experimental runs are expensive or time consuming (as with crash tests for example). In such cases, if the probability for a factor to be influent is very low (less than 10%, which is called the "sparsity effect"), a supersaturated design may be considered. In this design the number of effects to be estimated is higher than the number of experiments. This kind of design is less expensive and time consuming than classical screening matrices.

First developed in the 1950s by Satterthwaite [2] as a random balance and Booth and Cox [3] in a systematic manner, these designs have recently become increasingly popular. Nevertheless, most studies have focused on two-level supersaturated designs (see for example [4–19]), with several extensions to three-level [20,21] or multi-level [22,23] supersaturated designs. Much more recently mixed-level supersaturated designs were tested [24–28], and were found adapted in cases when the response is based on a polynomial response surface model or in situations where factors are categorical variables.

In this project, realized in the Chemical Development Automation Laboratory of Sanofi-Aventis in Vitry sur Seine, a mixed-level supersaturated (asymmetric) design was carried out in order to estimate the robustness of an organic synthesis. A 12-run supersaturated design was constructed, allowing us to screen 17 two-level factors and 5 three-level factors. As this mixed-level supersaturated design is not conventional and has seldom been studied, a 40-run screening matrix (D-optimal, [29]) was built in order to compare the results. This matrix was a complement of the supersaturated design: all of the experiments of the supersaturated design were included in this D-optimal matrix.

2. Application of a supersaturated design to an organic synthesis

2.1. Synthesis

The study applies to the industrial synthesis of PBA salt, an intermediate of synthesis of an anti-cancer drug. A mixed-level supersaturated design was carried out in order to evaluate the influent effects on the process, and more especially the purity of the salt obtained.

2.1.1. Reaction

The PBA salt is made using the reaction presented in Fig. 1.

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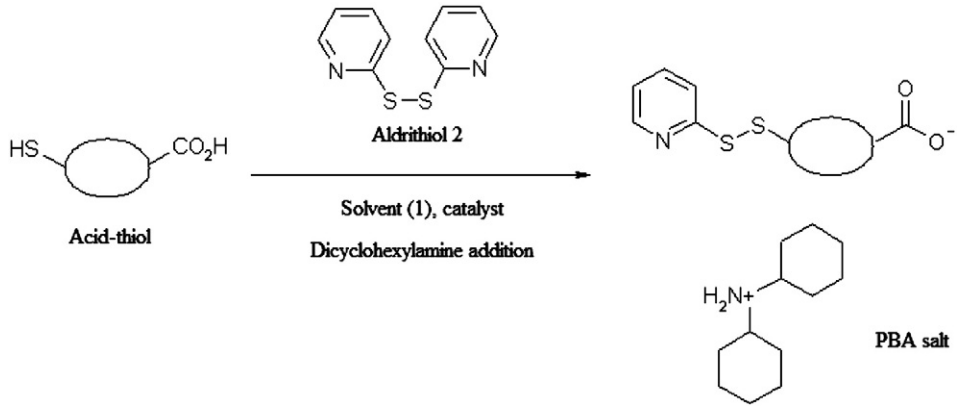

Fig. 1. Synthesis reaction.

2.1.2. Protocol

2,2′-Dithiopyridine (1.5 eq) was dissolved in a solvent (1) (5 V/dithiopyridine) and stirred for 10 min. The solution was cooled down to 0 ± 3 °C, and a catalyst added (0.02 eq). A solution of acid-thiol (1 eq) was then added at a temperature below 3 °C. The reaction mixture was stirred for 5 h at 0 ± 3 °C and then concentrated under reduced pressure to half its initial volume V_0. The concentrated mixture was stirred for 1 h at 0 ± 3 °C and the precipitated by-product (thiopyridone) was isolated by filtration. Dicyclohexylamine (1.2 eq) was then added to the mother liquor at 15 ± 3 °C, and the mixture cooled down to 0 ± 5 °C. The mixture was then stirred for 5 h at 0 ± 3 °C. The solid product (dicyclohexylamine salt) was isolated by filtration, washed with solvent (1) (2 × 12.5 V) and dried under reduced pressure at 40 °C. The purity of the dried product was determined by HPLC.

This basic protocol was adapted to each experiment, in order to allow the variations of the studied factors.

2.1.3. Equipment

All experiments of the supersaturated design and some of the D-optimal design were carried out using a multi-reactors Polyblock H.E.L®, piloted by WinIso software, and reactors volumes were either of 150 mL or 100 mL capacities. The Polyblock can receive 4 reactors independently controlled in terms of temperature and stirring. Some of the experiments of the 40-run were done on an Auto-MATE H.E.L®, also piloted by WinIso, using 100 mL and 50 mL reactors. The purity of the obtained salt was then determined by an HPLC analysis, using a Waters® Alliance equipped by an XTerra RP8 150 * 4.6 mm–3.5 μm column. Data acquisition was made via Waters Empower® software. Results were obtained thanks to an external calibration, by comparison of the sample's chromatogram to a known standard, considered 100% pure. 20 μL of sample solution were eluted by a mixture of acetonitrile and water at 1 mL/min flow for 35 min, and analysed in UV detection, at 290 nm.

2.2. Experimental design

2.2.1. Factors and domain of interest

In this study, 22 factors were studied, and one response (the purity of the isolated salt) was analysed. The factors were chosen based on the reference protocol. Three different suppliers were used for each of the reagents and three different catalysts were tested. Factors and levels are shown in Table 1 in which eq is the molar equivalent in acid-thiol, V is volume in mL per g of dithiopyridine and V_0 is the initial volume.

One response, the purity of the PBA salt, was analysed using the supersaturated design.

2.2.2. Construction of the supersaturated design

The mixed-level supersaturated design ($N = 12$) was constructed according to Yamada [24] using C_2 and D_3 designs (constructed by lexicographical enumeration and computer search respectively) in association with the generating designs $T^2{}_2$ and $T^2{}_3$, also proposed by Yamada [24]. These matrices are presented below.

$$C_2 = \begin{pmatrix} 1&1&1&1&1&1&1&1&1&1\\ 1&1&1&1&2&2&2&2&2&2\\ 1&2&2&2&1&1&1&2&2&2\\ 2&1&2&2&1&2&2&1&1&2\\ 2&2&1&2&2&1&2&1&2&1\\ 2&2&2&1&2&2&1&2&1&1 \end{pmatrix} \qquad D_3 = \begin{pmatrix} 1&1&1&1&1\\ 2&1&2&3&3\\ 3&2&3&3&1\\ 1&2&2&2&2\\ 2&3&3&1&2\\ 3&3&1&2&3 \end{pmatrix}$$

$$T^2{}_2 = \begin{pmatrix} 0&0\\ 0&1 \end{pmatrix} \qquad T^2{}_3 = \begin{pmatrix} 0&0\\ 1&2 \end{pmatrix}$$

A matrix $C = T^2{}_2 \oplus C_2$ is then generated, in which the operator $\oplus$ determines the $((i-1)lm+u,\ (j-1)p+v)$ element of the matrix C by $mod(t_{ij}+c_{uv}-1,l)+1$, with l number of levels of $T^2{}_2$ (in this case $l = 2$), m number of levels of $T^2{}_3$ (here $m = 3$), p number of

Table 1
Factors and experimental domain of interest.

	Factors	Number of levels	Level 1	Level 2	Level 3
U1	Dithiopyridine quantity	2	1.47 eq	1.53 eq	
U2	Solvent quantity	2	4.5 V	5.5 V	
U3	Stirring time 1	2	5 min	15 min	
U4	Temperature 1	2	−3 °C	+3 °C	
U5	Acid-thiol quantity	2	0.98 eq	1.02 eq	
U6	Acid-thiol adding time	2	5.5 min	16.5 min	
U7	Catalyst quantity	2	0.01 eq	0.03 eq	
U8	Stirring time 2	2	4.5 h	5.5 h	
U9	Concentration: end volume	2	0.4 V_0	0.6 V_0	
U10	Rinsing 1	2	0.14 V	0.16 V	
U11	Washing 1	2	0.48 V	0.53 V	
U12	Rinsing 2	2	0.14 V	0.16 V	
U13	Temperature 2	2	12 °C	18 °C	
U14	Dicyclohexylamine quantity	2	1.17 eq	1.22 eq	
U15	Dicyclohexylamine dosing time	2	7.5 min	22.5 min	
U16	Temperature 3	2	−3 °C	+3 °C	
U17	Washing 2	2	1.43 V	1.58 V	
U18	Dithiopyridine supplier	3	Alfa Aesar® 98%	Aldrich® 98%	Acros® 98%
U19	Solvent supplier	3	SDS® 99.8%	Acros® 99.5%	Prolabo® 99.9%
U20	Catalyst type	3	Catalyst 1	Catalyst 2	Catalyst 3
U21	Dicyclohexylamine supplier	3	Acros® 99%	Alfa Aesar® 98%	Aldrich® 99%
U22	Stirring time 3	3	15 h	18 h	23 h