Application Note:
The use of statistical experimental design in process optimization

Introduction:

As in all thriving areas of industry, Process Development Chemists face increasing pressures to carry out their work quicker and more efficiently. Today's Chemist has to carry out safe and rapid process development and to deliver the most economic process from the smallest number of laboratory experiments.

This application note describes a case study completed by HEL to demonstrate how a straightforward experimental design approach and a miniature computer controlled multiple reactor system can be used to reduce the manufacturing costs of a commercial chemical process. The process investigated was the pilot plant scale manufacture of 1,3,5-triphenylbenzene.

The Reaction:

The reaction route selected was via a series of aldol condensations. The process had been developed by the classical method of varying one variable at a time and several batches of material were produced on pilot plant scale by a UK fine chemical manufacturer.

Three moles of acetophenone undergo aldol condensations with subsequent elimination of water. The reaction is catalysed by anhydrous hydrogen chloride gas, which is believed to both catalyse conversion of acetophenone into its enol form and to protonate other acetophenone molecules to give a protonated species with which the enol can react. Triethyl orthoformate (TEOF) is also employed, which is hydrolysed by the water formed. Absolute ethanol is used as the reaction solvent.

The Process:

A solution of acetophenone and TEOF in absolute ethanol is gassed with anhydrous hydrogen chloride at 30°C. The hydrogen chloride is gassed at such a rate as to give a fast, controllable, exothermic reaction. The product precipitates out and the resulting slurry is cooled and then centrifuged.

The amounts of hydrogen chloride and TEOF were thought to affect the product yield and hence an excess of these reagents were used in the process; 1.5 molar equivalents (with respect to acetophenone) of hydrogen chloride and 1.2 molar equivalents (with respect to acetophenone) of TEOF were employed.

Processing under these conditions was found to give an isolated product yield of ~55%. This moderate yield was due to incomplete reaction rather than the formation of by-products from competing side reactions.

Strategy of Optimisation:

The approach adopted was to use statistical experimental design to determine the key process variables and maximise the isolated product yield. The experiments were carried out in a four-reactor auto-MATE, HEL's miniature, computer controlled, multiple reactor system designed for development and optimisation of batch and semi-batch processes. This enabled four experiments to be run simultaneously, experiments with highly reproducible results.

The following variables were initially identified as potentially important in the process:

- ▲ The amount of TEOF
- ▲ The amount of hydrogen chloride
- ▲ The reaction temperature
- ▲ The reaction solvent

An initial 2-factorial screening design was used to identify which, if any, of these variables had a statistically significant effect on the product yield. This generated sixteen experiments to be carried out at high and low variable levels. For the numerical variables, these levels were set at 50% above and below the standard process values. The choice of reaction solvent levels was a bit more complicated - not being a quantitative value.

Temp. (°C)	Molar Equiv. of HCl	Molar Equiv. of TEOF	Solvent	% Yield
15	0.75	0.6	IPA	0
15	2.25	0.6	IPA	0
45	0.75	1.8	IPA	33.2
45	2.25	1.8	IPA	38.2
15	0.75	1.8	IPA	28.9
15	2.25	1.8	IPA	37.8
15	0.75	0.6	n-BuOH	0
15	2.25	0.6	n-BuOH	8.3
15	0.75	1.8	n-BuOH	0
15	2.25	1.8	n-BuOH	24.5
45	0.75	0.6	IPA	0
45	2.25	0.6	IPA	7.4
45	0.75	0.6	n-BuOH	13.7
45	2.25	0.6	n-BuOH	19.9
45	0.75	1.8	n-BuOH	27.5
45	2.25	1.8	n-BuOH	27.9

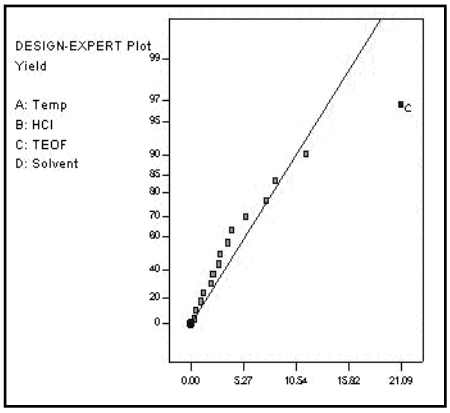
Table 1: Summary of 2-factorial design

Many other common organic solvents had previously been investigated and it was concluded that other alcohols were the only realistic alternatives to ethanol. Methanol had already been tried unsuccessfully and was found to give reduced product yields of 30 to 35 %. Hence propan-2-ol (IPA) and butan-1-ol (n-BuOH) were selected as possible alternatives.

Results:

These experiments and the product yields obtained are summarized in table 1. The results on the face of it do not look encouraging. In several cases no product was obtained and in the best case only a 38% yield was obtained. A casual glance at the data does not reveal obvious trends and only statistical analysis allows the single and multi-factor interactions to be determined. Analysis by statistical techniques of these results showed that the only variable found to have a significant effect on the yield was the TEOF level. This is demonstrated graphically in figure 1.

Figure 1: Half normal probability plot.



The figure shows the variable and interaction effects as a half normal probability plot where insignificant effects fall in a line and significant effects fall outside the normal distribution and hence deviate from the straight line.

It can be seen that the only point deviating significantly from the straight line is that which corresponds to the TEOF. Thus, the amount of TEOF was the only variable to have a statistically significant effect on the product yield. The remaining unlabelled points, that represent the remaining three variables,

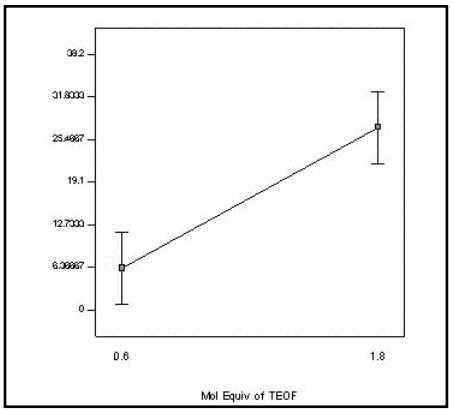


Figure 2: Plot of yield vs high & low level of TEOF

and all the combinations of the four variable interactions, do not deviate significantly from the straight line and have little effect on the yield.

Figure 2 shows the effect of TEOF in more detail. It can be seen that the TEOF exerted a positive effect i.e. as we move from the low value to the high value the yield improves.

Conclusions:

From the results of the initial screening design a number of conclusions can already be drawn, some of which offer cost savings.

Of the four variables investigated only the amount of TEOF has a significant effect on yield with the optimum amount yet to be determined.

It was concluded that the reaction temperature should remain at ~30ºC, since higher temperatures had no beneficial effect on the product yield and that the amount of hydrogen chloride used can be reduced by half without any detrimental effect on the product yield. This represents a significant cost saving and improves the economics of the process by reducing the usage of hydrogen chloride and reducing the sparging time from nine hours to less than five hours (if the gas flow rate remains unchanged). It may be possible to reduce the amount of hydrogen chloride further but this has not yet been investigated.

With regard to the choice of reaction solvent, statistical analysis showed the two solvents used not to have a significant effect on the product yield and hence in theory either solvent could be chosen. However this is unwise since it was observed that the percentage yields from all the reactions were less than for the standard operating process and in several cases no product at all was isolated. This rather crudely demonstrates how interpretation of the results is important. We have to remember to compare the results to that of the standard process using ethanol. The reaction did not proceed well in either of the two different alcohols chosen and it was concluded that ethanol should remain as the solvent of choice.

TEOF Optimisation

With only a single variable to optimise further more detailed experimental designs such as a full composite design were not necessary. It was now a straightforward case of carrying out experiments over a range of TEOF quantities. The product yields from these experiments are shown graphically in figure 3.

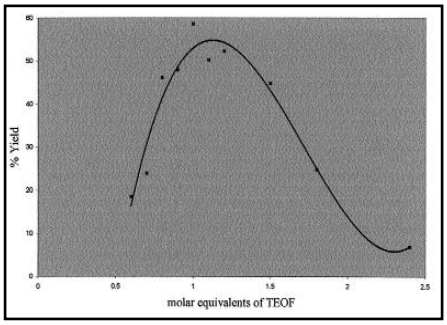


Figure 3: Plot of % yield vs amount of TEOF

The plot shows that the data gives a roughly normal Gaussian distribution with a maximum yield of ~60% seen with an equi-molar amount of TEOF. Thus, we can now conclude the optimum amount of TEOF is at 1.0 molar equivalent, which represents a ~17% reduction compared to the original process and gives about a ~5% higher yield.

Recommended Process Changes:

It was recommended that the amount of TEOF employed is reduced to 1.0 molar equivalent and that the amount of hydrogen chloride is reduced to 0.75 molar equivalents. It is believed that these changes will give a higher product yield with reduced usage of hydrogen chloride and TEOF and a shorter processing time. A modest increase in batch size will also be possible. It was estimated that the combination of these relatively small changes will result in a ~20% saving on the manufacturing cost of 1,3,5-triphenylbenzene relative to the current pilot scale process.