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Still Crossing the Chasm: Chemical Engineering Modeling in Drug Discovery and Development

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Abstract

Remarkable success applying chemical engineering tools to pharmaceutical process Research and Development has been obtained. Despite this, only early adopters of innovation seem to have widely accepted such methods for drug discovery and development. There are still some who must be convinced that by using chemical engineering science, better, faster and cheaper drug discovery and development can be accomplished. Two successful examples of chemical engineering modeling, in support of pharmaceutical process engineering are shown here: 1) a fast competitive reactive system, Bourne III, was successfully scaled-up from a reactor calorimeter (RC1) to a geometrically non-similar kilo-lab reactor using mixing-based scale-up modeling; 2) an active pharmaceutical ingredient crystallization process tolerance study was executed using statistical modeling. The crystallization process, developed based on several DoE matrices, was then successfully scaled-up to the pilot plant, producing 100 kg of drug substance passing all specifications.

Keywords

Scale-up, mixing, active pharmaceutical ingredient (API), crystallization, process development, process tolerance, critical process parameters, fast competitive chemical reactions, Bourne III, reactor calorimeter, RC1, statistical design of experiments, DoE.

1. Introduction

Computer aided process engineering industrial success stories can be found in the open literature, albeit, because of confidentiality concerns, fewer than academic accounts. For example: an interesting review, discussing modeling in chemical engineering as a tool for process innovation, was recently published[1]; the use of modeling tools in the industrially important scale-up of active pharmaceutical ingredient (API) crystallization processes was reported[2].

After the announcement of the risk-based, Quality by Design (QbD) manufacturing practices by the Food and Drug Administration (FDA), more sustained efforts were invested in process modeling. The use of Process Analytical Technologies (PAT) provided an excellent opportunity for the rapid advancement of chemometric techniques. A recent example of success with an industrial PAT applications was reported[3].

More established areas of process modeling for solving industrial problems include: mixing and scale-up[4], kinetic modeling[5], and statistical modeling for process optimization[6]. A review covering several emerging technologies in pharmaceutical process research and development was published[7]; therein, special emphasis is given to parallel experimentation and screening.

Based on all these encouraging accounts, one could assume that process modeling is an "automatic" tool invoked by pharmaceutical process scientists. Unfortunately, for a variety of reasons, the reality is different.

Perhaps because most organizations are risk-averse, and also because of the mathematical component in process modeling, and because of the complexity of research and development metrics, implementation of process modeling is met with some resistance. In addition, the drive to reach the "desired state"[8], where process design ought to be based on first principles, can be in conflict with the inevitable simplification needed in modeling practice.

From a marketing perspective, Moore described the barrier in adopting new technologies as a "chasm"[9]; this chasm exists between the innovators and the early adopters of new technologies, and all others (the early and late majority, and the proverbial "laggards"). Once the chasm is crossed, adoption of new technologies is expected to accelerate rapidly. Proof of robustness and reliability of the new technologies are expected to accelerate the crossing of the chasm.

With the current pressure imposed on the pharmaceutical industry to increase the number of commercialized new molecular entities at lower costs, the hope is that process modeling will eventually find its well deserved place in the process scientists' tool box.

2. Problem Statement, Background

Two case studies are presented in this paper: the scale-up of a fast competitive reactive system, and an Active Pharmaceutical Ingredient (API) crystallization process tolerance study.

2.1 Rapid Scale-Up Factor Determination: the Case of a Fast, Competitive, Parallel Reactive System (Bourne III)

Fast competitive parallel reactions executed in batch agitated reactors are frequently practiced in the pharmaceutical industry. The Bourne III system contains a pair of parallel competitive reactions: an acid-base neutralization, and an ester hydrolysis reaction. The Bourne III system is of direct relevance for organic processes, such as the pH adjustment in systems containing pH-labile organic compounds. The Bourne III is executed by adding a concentrated aqueous solution of sodium hydroxide to a mixture of concentrated aqueous hydrochloric acid and ethyl-chloroacetate. If mixing is very good, only the neutralization process occurs, because it is much faster than the ester hydrolysis. If mixing is "imperfect", ester hydrolysis also occurs, and the amount of ethanol formed is an indication ("fingerprint") of the quality of mixing in the reactor.
Recently, Merck scientists used the Bourne system for the design and characterization of pilot plant reactors. The goal was to develop a fast, reliable procedure to scale-up the Borne III, to reactors that are non-geometrically similar to their small scale counterparts.

2.2 Active Pharmaceutical Ingredient (API) Crystallization Process Tolerance Investigation

Production of a Phase I/II API was designed to be executed in a three-step process: i) diastereomoeric resolution, ii) free-basing, and iii) salt-formation, and non-seeded crystallization of the API. During one calendar year, the chemical process research team developed preliminary processes for all the steps, showing success one time in the kilo-lab. The process then had to be demonstrated in the pilot plant (100 gal scale). Of the first three batches, only one produced API that passed specifications. Failure in the pilot plant was due to excessive OVI-IPA (organic volatile impurities, for iso-propanol), and as understood later, also due to the presence of a polymorphic impurity.
The campaign was aborted, and an engineering development team was chartered to troubleshoot the process, develop a robust alternative and, more importantly, to produce 100 kg of API of acceptable quality in two months (using resources of approximately four person-months).

3. Paper Approach

3.1. Methodology

The Bourne III Case Study

The Bourne III reactive system has been extensively investigated in the past ten years and was also used to design pilot plant equipment[10]. This is a reactive system comprised of two reactions, one extremely fast (k_1=1.3 x10^8 m^3 * mol^{-1}* s^{-1}) acid-base neutralization, the other a slower basic ester hydrolysis (k_2=0.03 m^3*mol^{-1}*s^{-1}). Under ideal mixing conditions, no ester hydrolysis should occur. Under typical non-ideal mixing conditions, some ethanol formation can be observed.

$$HCl + NaOH \xrightarrow{k_1} H_2O + NaCl$$

$$CH_2ClCOOC_2H_5 + NaOH \xrightarrow{k_2} C_2H_5OH + CH_2ClCOONa$$

A fundamental understanding, based on first principles, of the impact of the equipment characteristics (mass and heat transfer) on process results, such as selectivity (which in this case can be described by the amount of ethanol produced) is very difficult. In addition, even an incomplete solution would require a significant amount of resources, often unavailable in an industrial context. A semi-quantitative understanding of the reaction zone and its scale-up [11] was executed, and will be reported elsewhere..

A significant amount of information is available for Bourne III, such as: reaction kinetics, impact on process results of stoichiometry, addition point, and addition rate/ mesomixing time. In such a case, a practical approach for process transfer uses scale-up modeling. Scale-up modeling is based on scale-up factors, i.e. process parameters that must either be kept constant, or changed in a prescribed way upon scale-up. Several process parameters can be considered as scale-up factors; such as: power per volume, tip velocity of the agitator, macromixing time[12], micromixing time, etc. We must also keep in mind that depending on the operating conditions chosen, scaling-up a reactive system may use different scale-up factors. Our goal was to determine the scale-up factor for the Bourne III system, when surface addition is used.

Process parameter calculation can be accomplished using mixing-based models. Several databases are available and many large organizations have developed proprietary models. A useful, commercially available package is VisiMix™; the flow of the calculations is described in Figure 1 below[13].

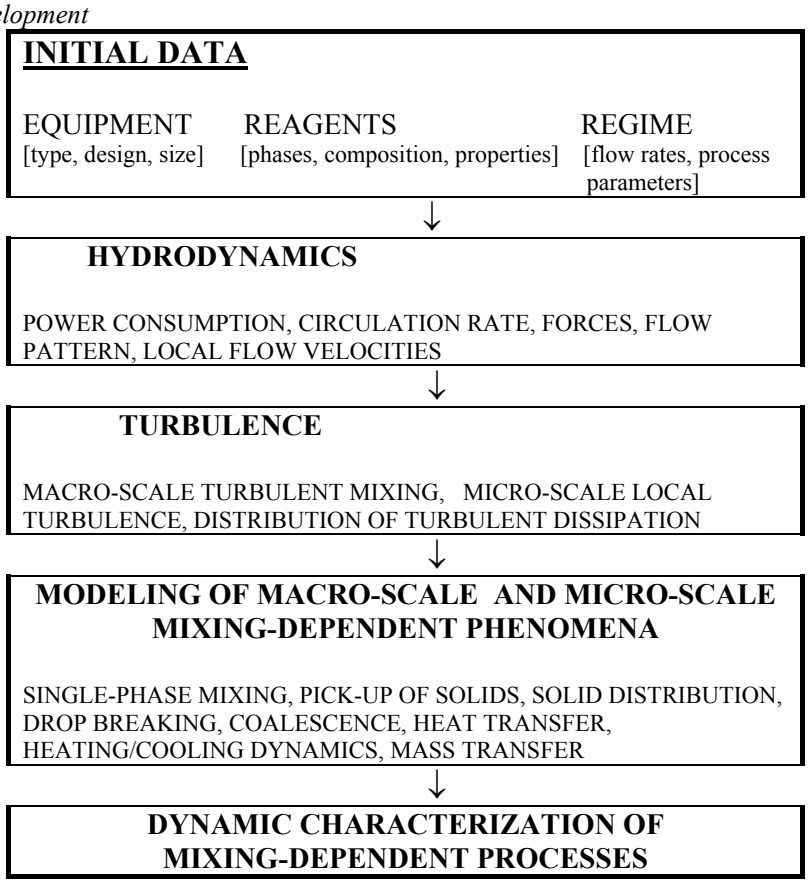

Fig. 1. Calculations flow in the VisiMix™ software program

An important advantage of the VisiMix™ platform is the fact that the software program uses the synergy between theoretical calculations and empirical modeling. Experimental verification of the models developed is based on literature data and the authors' work in the former Soviet Union, during the second half of the twentieth century.

Another approach, that we also attempted in this project, without success, is the use of the Damkholer number for scale-up[14].

Further insight into mixing processes is now possible using sophisticated CFD code. In spite of the industrial success of CFD modeling in several industries, the pharmaceutical industry is still evaluating this tool. The relatively expensive ownership and operation (skilled modeling experts are typically needed to perform the calculations and interpret the results), together with required the

experimental validation, are often quoted as challenges for the broader use of CFD modeling in pharmaceutical process research and development.

The API Crystallization Process Tolerance Case Study

A fundamental, first principles-based approach for the design of an API crystallization process is a very complex task[15]. For drug candidates in early stages of development, there is an insufficient amount of physico-chemical data to support crystallization process design even partially based on first principles. In an industrial context, especially before commercialization, such a fundamental approach would require an unrealistic amount of resources.
For this study, the process results considered were yield, purity, organic volatile impurities (OVI) and polymorphic purity. A key objective of this investigation was process robustness. Hence, we had to understand what were the critical control parameters of the process (CPP), parameters that must be narrowly controlled in order to produce API of acceptable quality attributes. Successful scale-up of the crystallization process had to be demonstrated at kilo-lab and pilot plant scales[16].
A practical approach for the development of a crystallization process for a drug candidate in Phase I/II, when process robustness is important, relies on statistical modeling. Statistical design of experiments is now used in process research and development, however mostly for process optimization. The statistical approach (DoE) is a highly reliable method to identify critical process parameters (CPP). The most important benefits of statistically designed experiments are that they provide a strict mathematical framework for changing all pertinent factors simultaneously, and that they achieve this in relatively few experiments.
The development of this API crystallization process was based on several DoE matrices. One of the DoE matrices is described here, showing how we assessed the crystallization process tolerance with respect to solvent composition. Process tolerance must precede process validation, the step taken before a commercial process for an API is “locked”. Through process tolerance investigations we determine the recommended (desirable), and the acceptable ranges for the critical process parameters. A separate investigation of agitation rate and temperature was also conducted. Neither parameter was identified as critical, but agitation rate (turbulent shear rate), was found, as expected, to impact the API particle size and agglomeration level.

3.2 Experimental

All the experiments described herein were executed in an automated laboratory reactor-calorimeter (RC1), AP01 (2 liters), from Mettler-Toledo AutoChem[17]. The RC1-AP01 characteristics are: inside diameter = 140 mm; total tank height

= 160 mm. The impeller characteristics: glass pitched blade, tip diameter = 76.2 mm; four blades, pitch angle = 45 ^{o}; width of blade = 6 mm; clearance from the bottom: 30 mm; motor power: 367 W. The reactor was fitted with two thermal probes that acted as baffles, of 10 mm width each, positioned 15 mm from the wall, and 120 mm from the reactor bottom, with a nearly perpendicular positioning to the plane of the reactor bottom.
The mixing and scale-up calculations were executed using the turbulent module of VisiMix ™ (VisiMix 2k2+ Turbulent)[18].
The average properties of the media used in the calculations were as follows: Newtonian media, average density: 955 kg/m^3, kinematic viscosity = 1.367 m^2/s, dynamic viscosity = 1.23 cP (0.00123 Pa*s); the density of the liquid phase = 900 kg/m^3; concentration of solid phase = 100 kg/m^3, density of solid phase = 2,000 kg/m^3, average particle size = 100 μm, size of largest particles = 200 μm.
The statistical designed experiments were planned and analyzed using two platforms: the JMP software program (v. 6.0) from the SAS Institute[19], and the DoE FUSION PRO™ (v. 7.3.20) from the S-Matrix Co[20].

The Bourne III Procedure

a. Charge the reactor with a suitable amount of de-ionized water, start the RC1 imposing constant temperature in the reactor (21 ^{o}C)
b. Charge the RC1 with a suitable 1:1 mixture of ethylchloroacetate and concentrated aqueous HCl; homogenize (at high agitation speed if needed)
c. Set the RC1 agitation speed as planned
d. Start adding the equivalent amount of concentrated (5M) sodium hydroxide at 2 mL/min (slow surface addition)
e. Sample and rapidly analyze (GC) the amount of ethanol present in the reaction mixture.

Reagents: Ethylchloroacetate $CH_2ClCOOC_2H_5$ of 99 % purity was used (Aldrich). NaOH fresh solutions were prepared from NaOH pellets of 99% purity (Aldrich). HCl was used as 37 % aqueous solution (Aldrich).

The API Crystallization Procedure

The crystallization process requires for the crystallization solvent composition (wt %): 89.0 % IPA, 8.0 % MTBE, 3.0 % water. This process includes the following steps:

a. Dissolve the chiral free-base at 0.20 M in a IPA/MTBE solvent mixture (90.5% IPA, 9.5% MTBE, wt. %) at 50 ^{o}C

b. Add the chiral acid in an equivalent amount, dissolved at 3M concentration in an IPA/water (74.8% IPA, 25.2% H_2O, wt.%) solvent mixture
c. Cool the reaction mixture to 0 C ^oC at 0.25 ^oC/min
d. Filter, wash, and dry (in vacuo, 40 ^oC)

Note: due to confidentiality considerations, the actual chemical structure of the API, its corresponding free base, and of the salt-former chiral acid cannot be disclosed here.

3.3 Results and Discussion

The Bourne III Case Study

The goal of this work was to establish a method which allowed the selection of batch size and agitation speed during scale-up, while reproducing the selectivity obtained at small scale. Such an approach is very practical for multi-purpose pilot plants, typical for the pharmaceutical industry. This study focused on the identification of scale-up factor/s, i.e. the determination of which process parameter/s must be held constant, or changed in a prescribed way to reproduce the selectivity upon scale-up. The published results of investigations related to concentration effects and addition times for the Bourne III system, were implemented in this experimental protocol.
Mixing calculations executed using VisiMix™ have allowed the design of the six experiment matrix in Table 1 below.

Table 1. Bourne III Experimental Design

	Input		***VisiMix ™ Calculated Process Parameters***				
#	Batch Size	Agitation Rate	Reynolds for Flow	P/m* max.	P/m ave.	Macro mixing Time	Micro mixing Time
	mL	*RPM*		*W/kg*	*W/kg*	*s*	*s*
1	900	180	6,050	1.1	0.010	6.3	21.4
2	900	360	12,300	8.5	0.090	3.1	7.6
3	900	420	14,400	13.5	0.150	2.6	6.1
4	900	520	17,900	25.5	0.285	2.1	4.4
5	1,800	350	8,960	11.8	0.065	6.5	5.7
6	1,800	400	10,300	17.6	0.097	5.8	4.9

*P/m = Power per mass.; ** Reynolds for Flow is not identical with Reynolds for the Impeller.

Note that experiments five and six can be deemed as "internal" scale-up experiments: experiment five was designed so that the macromixing time was comparable to the macromixing time of experiment one; experiment six was designed to reproduce the average power/mass in experiment two.

The corresponding results are depicted below. From the data analysis one can see that neither macromixing time nor power/mass are good candidates as scale-up factors in this study. For example, in experiment one, the ethanol yield was 24.7%, whereas in experiment five the yiled for ethanol was 18.6%.

Table 2. RC1 Experimental Results for Bourne III

#	**Batch Size**	**Agitation Rate**	**Ethanol**	**X(EtOH)**
	mL	*RPM*	*g/L*	*%*
1	900	180	1.86	24.7
2	900	360	2.10	27.8
3	900	420	1.65	21.9
4	900	520	1.50	17.9
5	1,800	350	1.40	18.6
6	1,800	400	1.35	17.9

Note: the standard error for the ethanol concentration measured was approximately 2%; X = yield of ethanol (%)

Interestingly, when conducting a control experiment (no HCl) the extent of ester hydrolysis was quite significant, producing ethanol in 92% yield.

When the data was analyzed in detail, the ethanol amount was found to correlate well with the micromixing time (Figure 2 below). Due to the transitional conditions ($Re_{flow} = 6{,}050$), the first experiment was deemed an outlier, and was not included in the regression analysis.

No meaningful correlation was found with either the power/mass or macromixing time respectively.

Careful consideration was given to turbulence at the addition point and an estimation of the reaction zone was also executed .

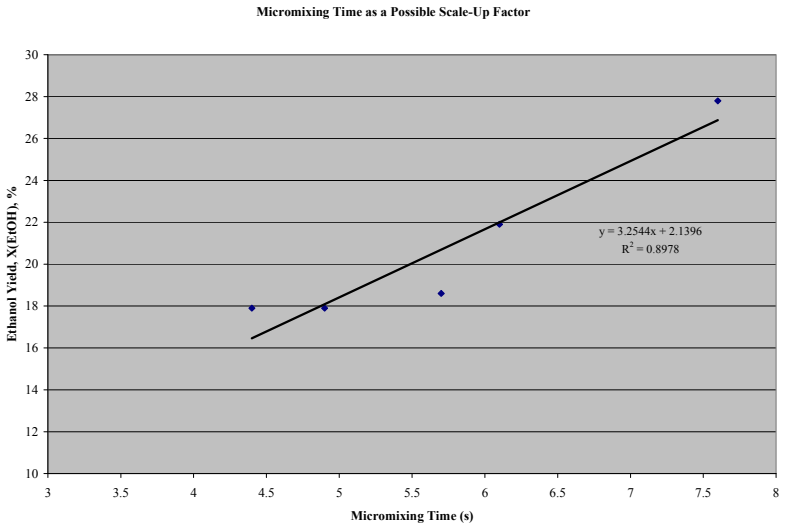

Figure 2. The ethanol yield obtained correlates well with the VisiMix ™ calculated micromixing time

Based on this finding, and using VisiMix ™ calculations for the kilo-lab reactor, the following scale-up scenarios were identified (Table 3).
The RC1 calculations were executed at two limiting agitation rates, with the higher agitation rate (520 RPM) leading to an acceptable selectivity (low amount of ethanol produced). Therefore the 520 RPM process conditions had to be "reproduced" upon scale-up.

Table 3. Scale-up Scenarios for the Kilo-Lab

	Process Parameter		**RC1**		**Kilo-Lab**			
Manipulated Variable	**Agitation Rate**	***RPM***	**180**	**520**	**115**	**130**	**320**	**460**
Calculated Parameters	**Power/mass, average**	*W/kg*	0.01	0.29	0.30	0.42	6.3	18.8
	Power/mass, max.	*W/kg*	1.1	25.5	12.0	17.3	258.0	765.0
	Macromixing Time	*s*	6.3	2.1	8.6	7.6	3.1	2.1
	Micromixing Time	*s*	21.4	4.4	5.0	4.2	1.1	0.6

Note that the reaction mass in the RC1 case is 1.0 kg, and 35.0 kg in the Kilo-Lab reactor (both are half full).

For equal macromixing time (2.1 s), a 460 RPM would be needed in the 70 L kilo-lab reactor. This agitation speed is higher than practical in the kilo-lab reactor (half-full). The highest realistic agitation rate in the 70L reactor is 320 RPM, and this experiment was included in the plan.

For comparable micromixing time (4.4 s), an agitation of 130 RPM in the 70L reactor was required. This experiment was also then included in the plan.

Lastly, for comparable average power/mass (0.29 W/kg), a 115 RPM agitation in the 70L reactor was required. This experiment was not included in the plan because the RC1 results showed that power/mass (average) cannot be a scale-up factor.

When the designed scale-up experiments were executed in the kilo-lab 70 L reactor, the results in Table 4 were obtained. These confirm that micromixing time is indeed a scale-up factor, as a four second micromixing time produced approximately eighteen percent ethanol at both scales, the RC1 and the Kilo-Lab. The experiment at 320 RPM confirms one of the limitations of the test system as described by Bourne: above 1 W/kg power per mass, the sensitivity to mixing is more difficult to detect.

Table 4. Bourne III Kilo-Lab Results

#	**Batch Size**	**Agitation Rate**	**Ethanol**	**X(EtOH)**
	L	*RPM*	*g/L*	*%*
1	35.0	130	1.43	17.3
2	35.0	130	1.67	20.2
3	35.0	320	1.34	16.2

It is significant to mention that the Bourne data[14] submitted to the same analysis, in spite of the simplification of the scale-up factor approach, confirmed micromixing time as a scale-up factor.

The API Crystallization Case Study

The crystallization solvent composition process tolerance DoE was designed varying the concentrations of the solvents as follows (wt. %):

- IPA 87.0-93.0
- MTBE 6.0-12.0
- H_2O 1.0-7.0

Note that for enhanced quality, the (mixture) design is symmetrical, i.e. the concentration range investigated for each solvent is 6 wt. %.

Other operational parameters: agitation, temperature, reagents concentrations were kept constant, and set at the values previously established.

The design used a model that included all main factors, and their two-way interactions while varying each factor at four levels. The G-efficiency of the design was 100 %.

The process results included in the analysis were: OVI and polymorphic purity. Particle size distribution was also measured for all the samples generated, in preparation for the development of a particle size distribution model.
The experimental matrix and the results are depicted in Table 5 below:

Table 5. DoE Matrix for the API Crystallization Process Tolerance Study

#	IPA	H_2O	MTBE	OVI-IPA	Polymorph Impurity	Yield*
1	*% wt.*	*% wt.*	*% wt.*	*%*		*%*
2	89.0	3.0	8.0	0.18	0	99.6
3	90.0	1.0	9.0	0.49	0	99.7
4	93.0	1.0	6.0	0.43	0	99.7
5	87.0	7.0	6.0	0.31	1	94.9
6	87.0	4.0	9.0	0.12	0	97.2
7	90.0	4.0	6.0	0.11	0	96.9
8	89.0	3.0	8.0	0.17	0	98.0
9	87.0	1.0	12.0	0.43	0	99.5

IPA = iso-propanol; MTBE = Methyl-*tert*-Butyl Ether.* Yield: uncorrected; in all cases the assay values were consistently 99.8% or better. Table 5 includes a portion of the data generated.
Detection of the polymorphic impurity was executed using X-ray Powder Diffraction (XRPD); because of the very low levels, this analysis was done non-quantitatively. For the statistical analysis, a zero-one surrogate quantitation was used, aiming at understanding only the trends of solvent impact on the presence of the polymorphic purity.
The maximum acceptable level for OVI-IPA is 0.50%. For the drug substance to pass specifications, no polymorphic impurities should be detected by XRPD.
Due to confidentiality considerations the complete analysis cannot be disclosed here.
The model developed was used to predict the process results when the suspected critical process parameter, water level in the crystallization solvent, was increased by 16.6 %, from 3.0% to 3.5%.
A confirmatory experiment was then designed and executed at the following solvent composition:

89.3 % IPA, 7.2 % MTBE, and 3.5 % H_2O.

At 3.5 % water the model predicts an OVI-IPA = 0.14 +/- 0.11 (at +/- 2 Sigma Confidence Limits), passing specification of OVI-IPA < 0.50 %.
The confirmatory experiment produced material that passed all specifications, in 98 % yield; no polymorphic impurity detected by XRPD, and OVI-IPA = 0.16 %, well within the prediction of the model.

Water, frequently a critical process parameter, proved not to be one in this process.

Optimization Analysis; Definition of the Acceptable Process Parameter Ranges (Solvent Composition)

In order to determine the acceptable ranges for the solvent composition, an optimization analysis was executed using DoE Fusion PRO ™ (see graph below).

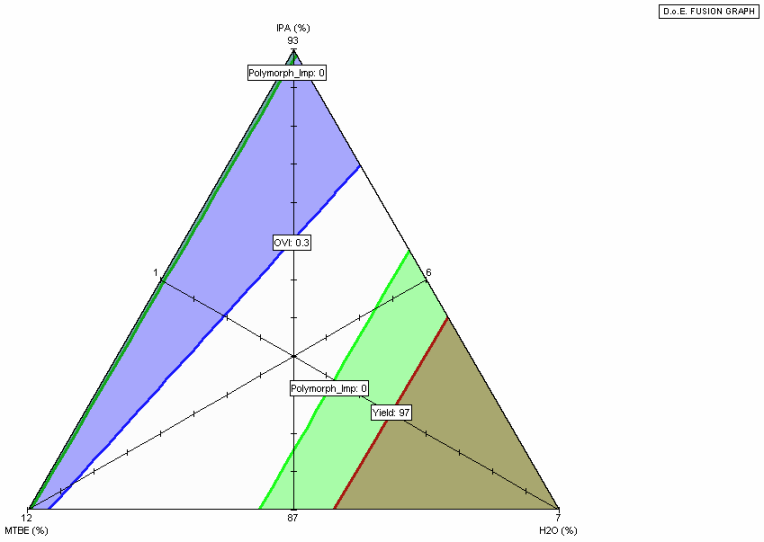

Figure 3. Optimization Analysis using DoE Fusion PRO ™; the white zone in the ternary diagram represents the desirable operating space, optimized for: OVI-IPA < 0.30%, pure polymorph (XRPD), and yield higher than 97%. The colored areas describe domains for which one or more of the optimization criteria are not met.

When analyzing for all the relevant process results (including particle size, not discussed here) the following desirable ranges were found (in wt %):

- ✓ Water: 1.5-3.5
- ✓ Iso-propanol: 88.0-92.0
- ✓ MTBE: 7.0-11.0

Under those conditions the following process results are predicted: OVI-IPA < 0.35%, pure form by XRPD, yield higher than 96%. We included the yield in this optimization calculation because water levels also impact yield (because of increased solubility of the API in water-rich systems).
Based on typical plant capabilities of charging solvents with +/- 4% accuracy, the magnitude of the desirable ranges defined above is more than sufficient. If

the OVI-IPA response is allowed to increase up to the specification limit (0.5%) and the yield to decrease to 90%, then *the acceptable ranges for solvent composition* become *(*wt %):

- Water: 1.1-3.6
- Iso-propanol: 88.0-93.0
- MTBE: 7.0-12.0

The crystallization process was then demonstrated at pilot scale: three batches were successfully produced, generating 100 kg of API passing all specifications, including pure form by XRPD, OVI-IPA consistently at only 0.20±0.02%, and at the expected yield (consistently at 96.5±0.5%). After Phase II investigations were initiated, process R&D work including particle size control was executed using the process knowledge developed during the "emergency intervention" described above.

4. Conclusions

Two successful examples of chemical engineering modeling, in support of pharmaceutical process engineering, were shown. A fast competitive reactive system, Bourne III, was successfully scaled-up from a laboratory reactor calorimeter (RC1), to a geometrically non-similar kilo-lab reactor using the VisiMix™ micromixing time as a scale-up factor. An API crystallization process tolerance study was executed using statistical modeling. The crystallization process, developed based on several DoE matrices, was then successfully scaled-up to the pilot plant, producing 100 kg of API passing all specifications.

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