# How To Minimise Scale UP Difficulties

**Dr Trevor Laird**

**Scale-up of chemical processes, particularly those involving batch or semi-batch manufacture is well-known to be a problematic area of chemistry and chemical engineering, and can be costly when it goes wrong. By correctly choosing and designing the synthetic route to a fine chemical or drug substance, as well as controlling the reaction and work up/product isolation parameters, many of the difficulties in scale up can be avoided. The more complex a process is in terms of chemistry and unit operations, the more there is to go wrong.**

**This article discusses what chemists and engineers can do in advance, both in the laboratory and kilo laboratory, to prevent or at least minimise scale-up issues.**

For robust and efficient scale-up it is important to choose good syntheses and this is often the decision of the chemist rather than the chemical engineer. One of the failings in university education of chemists is the teaching of organic synthesis from a discovery rather than a manufacturing perspective. In the latter approach, convergent synthetic routes using low cost raw materials, with a minimal waste output, suitable for scale up are designed. For the generic pharmaceutical industry – a major money-earner in India – it is essential to have the best synthesis (hopefully leading to the best process) to maintain price competitiveness; for the fine chemical, agrochemical, colour chemicals and flavour fragrance industries, this has always been the case, so the best examples of synthetic efficiency are often from these industries.

A simple example from the pharmaceutical industry is shown in **Scheme 1** for the manufacture of the key tetralone intermediate, used in most routes to make the Pfizer drug Sertraline, which is now off-patent. The original synthesis used for early manufacture compares unfavourably with a later 1-step process

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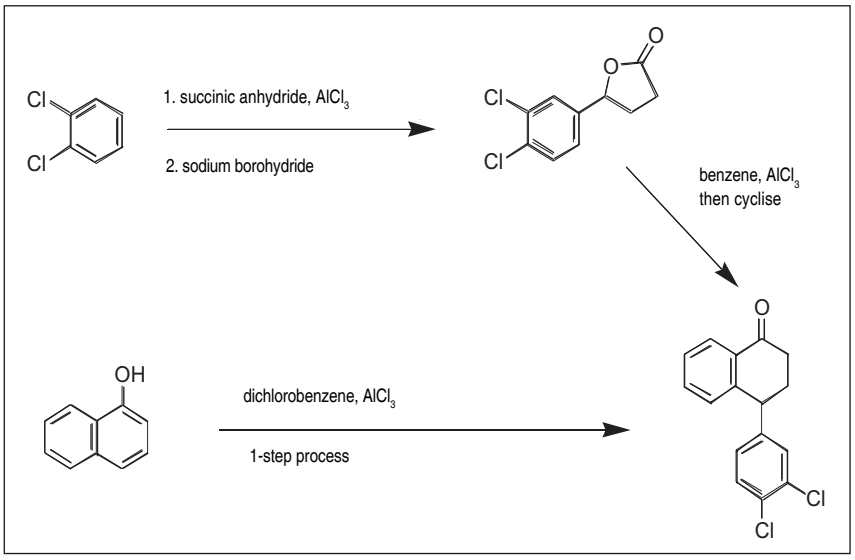
from the much cheaper raw material α-naphthol.[6]

**Scheme 1**




## Choosing appropriate conditions

To avoid scale up problems, it is important for chemists – with expert advice from chemical engineers – to choose the correct conditions to scale. Many chemists, however, believe that reaction selectivity can only be controlled by operating at low temperature, often at minus 78°C. Apart from the expense of cooling large batches to this temperature, there is a danger that the increased viscosity of the solvent, coupled with the low solubility of reactants/ products/ byproducts at this temperature, leads to reaction media which are difficult to mix on large scale and resulting in inhomogeneity in the batch with concomitant impurity generation. Encrustation of raw materials, intermediates and products on the vessel walls can also be a problem at these low temperatures.

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Whilst some batches occasionally do need such low temperatures, many processes can be operated at higher temperatures, provided the reagent is carefully dosed in to the process at the same rate as the reaction is proceeding. This ensures that the stoichiometry is constant throughout the addition.

## Correct dosing regime

Chemists are often vague about the meaning of stoichiometry in semi-batch processes, preferring to think only about the stoichiometry based on the reaction equation – for example the equation might say that 2 moles of A react with 1 mole of B to give the product C, and byproducts D. However, if reagent A is being added to a solution of reaction B in a stirred tank reactor, the stoichiometry in the reactor varies with time. The amount of product C formed along with by products D will depend on the ratio of A to B in the vessel at any one time, and this of course depends on the rate of addition of A, the rate of reaction of A with B [and this depends on the temperature, the solvent, the solvent purity (eg water content), concentration, pH, presence of catalysts or inhibitors etc.] and especially the mixing in the vessel, which may be scale dependent. Understanding the kinetics of the process, as chemical engineers usually want to do, will assist in the design of the process, allowing the correct choice of temperature along with the optimal dosing rate for that particular scale. For an exothermic reaction, of course, the dosing rate may be limited by the cooling capacity of the vessel. So it is important to understand exactly when the heat is generated in the process.

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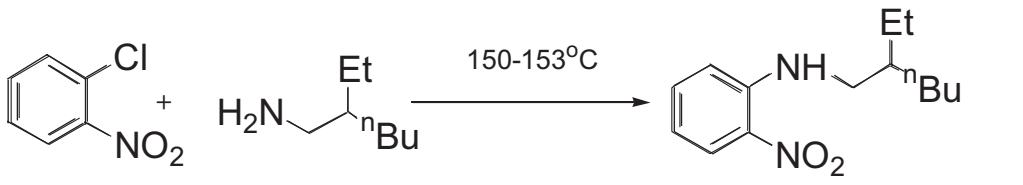
## Hazards of Scale Up

When scaling up chemical processes in batch reactors, there is always the potential for loss of control if the reaction is exothermic, since the change in heat transfer area per unit volume varies with scale. Whereas a laboratory 0.5L reactor has a heat transfer area of about $0.02m^2$, a production 3800L vessel has only $10.7m^2$; thus the heat transfer area per unit volume is $0.04m^2/L$ in the lab and only $0.0028\ m^2/L$ in the plant, a factor of 7 difference. The consequences of this are increased cycle times and particularly increased addition times for reagents. The question is usually whether these changes affect the yield and quality of the product – the answer often is yes!

Even more problematic is that if reagent addition is too fast compared to heat removal, accumulation can occur and can




**Scheme 2**

lead to a runaway reaction, especially if loss of cooling capacity occurs, simultaneously. The consequences may depend on whether decomposition of the reaction mixture then occurs (probably with gas evolution) and on the boiling point of the solvent used. Stoessel[7] has defined 5 classes of criticality with increasing hazard potential in his excellent article in OPRD, and more details of this topic can be found in this recent book[8]. Despite the widespread knowledge about the hazards of scale up, particularly of compounds with potentially hazardous groupings, such as nitro compounds, it is disturbing to see runaways still occurring due to poor hazard testing, and poor knowledge of the thermochemistry in the process.

**Morton International Inc after the explosion and fire, caused due to a runaway reaction that released flammable materials**

An example from 1998 at Morton International in USA, where an explosion and fire occured during the production of Automate Yellow 96 dye, is shown in **Scheme 2**, with a picture taken from the Chemical Safety Board report into this incident[9]. Hopefully lessons have been learned from this incident that batch (all in and heat) processes should be replaced with semi-batch operations (controlling the rate of addition of one component) whenever possible and that a change in batch size always needs a re-assessment of whether it is safe to carry out the process at the increased scale.

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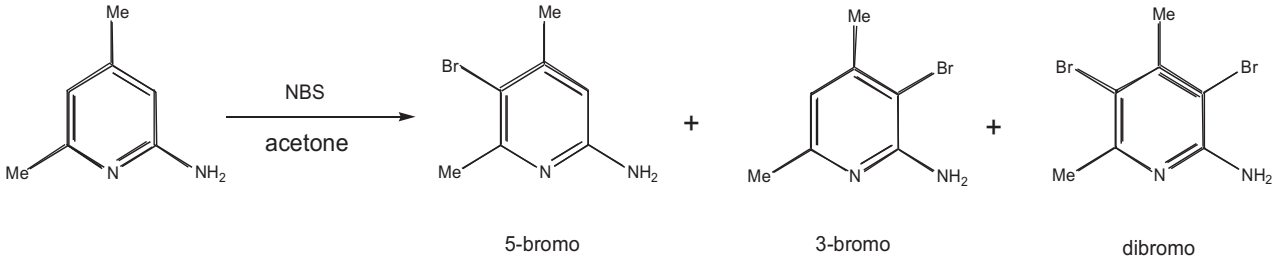
Companies who themselves have no hazard testing equipment, such as a reaction calorimeter or differential scanning calorimeter, can sometimes be reluctant to outsource the hazard testing to competent companies because of expense. They then risk scale up based on inadequate knowledge. From an accountancy viewpoint, destruction of a plant facility with possible loss of life affects the bottom line so much more than capital expenditure on calorimetric equipment, or a small contract for hazard evaluation. The spin-off from these studies is a better understanding of kinetics and by-product formation ; calorimetric evaluation can usually pay for itself since it usually leads to increased yield, quality or productivity.

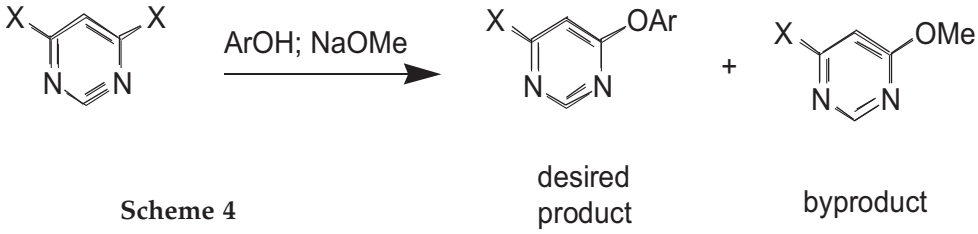
## Mass transfer issues

Chemists are often surprised when changes in selectivity occur on scale up, owing to differences in mass transfer across phases. An example from Merck (USA) is the solid dosing of N-bromosuccinimide (NBS) reagent to a heterocyclic amino derivative, where the selectivity differences on scale up are dramatic (**Scheme 3**). Solution addition of the NBS (NB acetonitrile is often the best solvent for this reagent) gives a better result but still the laboratory selectivity was not able to be matched[10].

When dosing solutions of

**Scheme 3**




**Scheme 4**

reagents in the laboratory, chemists usually add to the surface of the agitated liquid and this works fine on small scale. If this is done on the plant, however, poor mixing may occur in large reactors. The key is to add the reagents into a region of high turbulence, such as close to the tip of the agitator, using a dip pipe, or to add reagents via a recirculation loop. Ensuring that the temperature and viscosity of the added reagent is similar to that in the vessel will also aid in good mixing.

Scale up of agitation can be based on a number of factors but Paul[11] recommends using constant power per unit volume or mass. This mixing energy dissipation is given by:

$$E_i = NpN^3d^5/V$$

Where d = impeller diameter (m)
Np = power number
N = rotational speed ($sec^{-1}$)
V = volume ($m^3$)

Note here the dependence on the fifth power of the impeller diameter and the third power of the rotational speed, and it is easy to see why scale up can be problematic. One answer is to focus on scale down, with the mixing energy dissipa-tion being perhaps the most useful parameter for "scale down" experiments, i.e. mimicking the typical plant vessel in the laboratory at "bench" scale. The shape (height to diameter ratio) of laboratory vessels should also mimic those in the plant.

Even if a critical reagent is added via a dip-pipe close to the tip of the agitator, lack of selectivity may occur in fast reactions if the dip pipe diameter is too large, resulting in slow flow rate from the dip pipe into the bulk solution. In the example shown in **Scheme 4** the byproduct was formed owing to back-diffusion in the dip-pipe [12].

**If reagent addition is too fast compared to heat removal, accumulation can occur and can lead to a runaway reaction, especially if loss of cooling capacity occurs, simultaneously.**

Reactions involving two liquid phases, such as phase-transfer catalysed reactions, can also be very sensitive to the position of the agitator in the vessel, as well as the agitator type/diameter/shape, and differences in yield and quality of products may be seen depending on the choice of vessel. Guidelines have been advocated for scale up of such processes, such as "maintain the ratio of interfacial area to total volume a constant". Interfacial area is also significant during product isolations involving phase separations [13].

## Solvent extraction problems on Scale Up

During extractive work-ups in the laboratory, the chemist often does not record whether the aqueous phase was added to the organic, or vice-versa, since in the laboratory it usually makes no difference to the outcome of the experiment. In the plant, if the reaction mixture is organic and the vessel is not full, it may be convenient to add water to it, whereas if the vessel is full and a larger vessel needs to be used for the extractions, the water could be added first or last, depending on preferred

operations. The order of addition can make a big difference as to whether emulsions form, and to the time of disengagement of the layers, as well as their separation efficiency. Clearly this can affect yield, but also may impact on product quality, since a saturated solution of water in an organic solvent is an excellent hydrolysis medium for esters and other hydrolysable groups if traces of acid base are present. At extended separation times hydrolysis may then occur leading to greater amounts of by-products.

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For this reason the solvent ethyl acetate is a poor choice of extraction solvent for scale up, particularly in acid/base work-ups, since the extended times the ethyl acetate is in contact with water when trace acids/bases are present will initiate hydrolysis of the solvent, leading to more acid (acetic acid) which further catalyses hydrolysis. The high solubility of water in ethyl acetate and vice-versa means that aqueous layers, unless heavily salted, are rich in organics (and thus more difficult to dispose of) whereas the ethyl acetate layers have high water contents and may need drying before further processing. Isopropyl acetate and butyl acetate, though more expensive initially, may actually be more cost-effective overall in scale up, particularly since solvent recovery is easier because the low water content in the solvent leads to higher recoveries.

In the laboratory, liquid-liquid separations are carried out at ambient temperature, which varies from lab to lab! In the plant, depending on the its location and whether it is summer or winter, extractions may be carried at anywhere from 2-3°C to 40°C unless a temperature is specified, and different results from the laboratory will be encountered. Since extractions are more efficient at higher temperature and separations are usually better (no emulsions usually), it is often preferable on plant to extract in the 50-100°C range, if this is not detrimental to the product quality; it is certainly more efficient in both raw materials usage and time.

## Compatibility with glass, stainless steel and hastelloy

To avoid metal contamination, chemists mostly use glass equipment in the laboratory, but, for many reasons, engineers may prefer stainless steel or Hastelloy equipment in the plant and corrosion testing will be necessary to study compatibility. Many reaction mixtures, however, are incompatible with certain metals, even though the individual components may all be compatible in use tests. It is essential, therefore to use test the reaction mixture as well as the individual components for compatibility with the materials of construction of the vessel; one company I consulted for failed to do this and ended up with purple, rather than white product, when the reaction intermediate picked up iron from the reactor and formed a coloured complex!

In another case, one company failed to realise that a $CF_3$ group on an organic molecule may yield traces of HF in solution, formed in small amounts in byproduct processes. Since the reaction was being carried out in a glass-lined reactor, this equipment then became etched, and had to be removed from the plant and expensively relined before it was available for manufacturing use again and was a few months out of commission .

## Crystallisation and Polymorphism

Of all the unit operations which cause difficulty on scale up, crystallisation and drying are the most prevalent, particularly when the intermediate or final product is polymorphic or can form solvates[14]. Of course in India, the generic pharmaceutical industry is highly active in investigating alternative crystalline forms of drugs in order to circumvent existing patents, or to provide new IP opportunities. However, consistent manufacture of the desired form on large scale can be a problem. Key parameters controlling which form is produced, and the particle size distribution, (PSD, which determines filterability and drying times) include the number and level of trace impurities in solution (even as low as 0.01%), which may vary from batch to batch.

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Fine control of the crystallisation process (supersaturation, seeding, cooling profile, presence of impurities) leaves a lot to be desired, so batch to batch variations are expected. The control of a crystallisation process needs exact control of nucleation (by seeding at a defined supersaturation) and a

programmed cooling programme that allows the crystals to take up the supersaturation very slowly. Reactor or filter/centrifuge contamination from previous batches of the same substance may impact on the ability to produce the correct crystal form and PSD of the product. . These issues can also be relevant to the colour chemicals, agrochemicals and fine chemicals industries, where specific physical properties of the product are desired for further processing, such as formulation, or affect the stability of the product ( eg to oxygen or light).

The additional effect of stir out time/temperature on crystal form content and PSD, with a subsequent potential change during filtration/centrifugation (depending on choice and size of equipment) and drying (depending on dryer type, temperature, solvent removal etc) means that batch to batch reproducibility is never guaranteed. Only by careful laboratory studies of this interacting factors using statistical methods such as Design of Experiments can true manufacturing robustness be achieved.

## Optimisation using statistical methods

Many companies in India still carry out process optimisation using one parameter at a time variations, whereas the trend elsewhere is to use the Design of Experiments (DoE) approach, recognising that variables are rarely independent of each other ( eg rate of addition and temperature). In these detailed parameter studies it is important to study variables which affect scale up, such as dosing time and mixing, and parameters in the work-up and product isolation as well as in the reactions. Only by looking at the effect of all these interacting parameters can a truly optimised process, which works well on scale and is efficient and robust, be developed.

For pharmaceutical processes, regulatory authorities are keen to see the DoE approach used in new submissions, since it shows that "quality has been designed into the process" and gives assurance that the process is robust, and that the manufacturer knows the design space in which to operate and where the edge of failure lies. Such data is of course important and extremely useful for a plant manager operating any chemical process. Process understanding always leads to better process control and usually to more successful scale-up!

## Conclusion

The best way to minimise scale up problems is by data gathering and detailed process understanding. Having technical staff – both chemists and engineers – who are well trained with up-to-date knowledge of current thinking can help with design of better processes with fewer scale up issues. Using outside help in the form of consultants with industry experience can be invaluable for companies wishing to design low-cost processes which can be easily scaled up, and in trouble-shooting persistent manufacturing problems.

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***Editor's Note:***

*Scientific Update LLC regularly conducts conferences and training courses for industrial chemists and chemical engineers in chemical development and scale-up.*