INTRODUCTION

Transferring a process from small laboratory scale to full scale manufacturing presents obvious visible differences, even to those with limited scale-up and plant experience – it is correctly stated that transferring a process to commercial production is not simply a case of just using a larger beaker! However, there are some less visible, but equally important differences, in plant-scale operation that if considered in advance can help to ensure the technical transfer of a new process to commercial manufacture proceeds smoothly and robustly. The purpose of this technical piece is to examine a selection of these nuances and provide some awareness that can help shape a plant-ready process.

AGITATION

Anyone who has peered inside a vessel that is >1,000 L in volume whilst the agitator is running will recognise a stirred reaction mixture is a violent and turbulent place to be; yet it is often stated that agitation becomes less effective on scale-up. When going from gram-scale upwards, there is indeed a window of scale that can prove awkward; for which an overhead stirrer is too cumbersome, but a magnetic stirrer is ineffective (**Figure 1**). This window will vary depending on multiple factors, such as concentration, density, viscosity and homogeneity, but should not be of concern to anything above the kilo-lab scale.

Figure 1: Comparison of stirring between magnetic stirrer (**left**) and mechanical stirrer with impeller (**right**)

For example, stirring 50 mL of a given mixture with a 2 cm long stirrer bar at 700 rpm will generate power of 0.05 W/L. Stirring 5,000 L of the same mixture with a 0.5 m long agitator at 100 rpm will give 6.25 W/L – over 100 times more power per unit volume! Other measures beyond power, such as agitation rate, tip speed, torque and a host of dimensionless numbers (perhaps the most well known being the Reynolds number that points to laminar or turbulent flow) are also important in effecting good mixing. Consequently, stirring efficiency can be further increased by considering vessel design elements, such as baffles and impeller configuration, to provide greater turbulence, although this can be difficult to model on lab scale.

Whilst higher levels of agitation power generally have a positive effect on parameters such as reaction rate and conversion, some negative effects can result, such as emulsification of biphasic mixtures and a reduction in particle size, which may affect separations and filtrations. The most practicable way around this is to use a variable speed agitator, although this is not always a possible on a plant reactor.

$$A_{(sol)} + B_{(s)} \xrightarrow{\text{Solvent, } \Delta T} C_{(s)} + D_{(s)} + E_{(g)}$$

Figure 2: Hypothetical example

Consider the following hypothetical example (**Figure 2**). Where stirring is inefficient, it is possible that reagent **B** may be occluded within crystals of product **C** as it is formed, thus limiting conversion and potentially impacting quality. In this case, the extra attrition caused by more turbulent mixing may result in less entrainment (due to reduced particle size) and thus increased conversion. It is always important to consider the appropriate stirring regime in the laboratory (cf. **Figure 1**) before considering alternative physical or chemical options which may add unnecessary cost and complication.

TEMPERATURE CONTROL

That a larger reaction mass will take longer to heat up and cool down than a smaller one is clear; what is less immediately obvious is that the relative surface area falls as volume increases. This has a direct impact if impurities can be formed by thermal instability because a heated reaction mixture will spend much longer at elevated temperatures, since heating and cooling times may be measured in hours on

plant instead of minutes at lab scale. However, when it comes to dispersion of heat, during exothermic reagent additions for example, scaling a reaction may not be as straightforward to predict.

Returning to the example above (**Figure 2**), the change in concentration per unit volume of **A** is the same in both 20 g and 1500 kg scale reactions if both charges take the same time; and the heat sink provided by **A**, **B** and the solvent remains the same per unit volume. It is thus appropriate to balance the charge against a maximum temperature. Therefore, the cooling efficiency of the reactor will define the rate of addition, not the time taken on a small scale.

The appropriate operational temperature range (for example, T_{max} for an exothermic charge as described above) can be defined with a series of straightforward experiments, where **A** is charged at a variety of temperatures and the corresponding effect on conversion and impurity profile studied. The temperature range so defined will be of far more use when transferring the process to commercial scale production than the time taken to complete a charge on a smaller scale in the laboratory.

VAPOUR FLOW

Entrainment of solvent by vapour flow can lead to dramatic reductions in volume, particularly in reactions which require a constant nitrogen blanket, and cannot be ignored. However, reactions that produce molar equivalents of gaseous by-products will also have a similar effect, particularly in a reactor in which the action of the scrubber may result in a negative pressure applied to the vessel contents.

Entrainment of solvent may be beneficial for energy removal from a system if the solvent is returned to the vessel via the column or condenser (assuming the vessel has either); however, losses of either solvent or reagents can occur. Low boiling solvents, such as dichloromethane are avoided for this reason, as capture of entrained material is dependent on boiling point.

Figure 3: Distillation head

Consider the example again (**Figure 2**). If the addition is carried out close to the boiling point of **A**, the release of gas **E** may entrain **A** along with some of the reaction solvent. Thus, slow and/or poor conversion may result, or worse including contamination of the scrubber system and potential losses to the environment. These issues may not be seen in the lab for several reasons:

- Vapour is likely to be captured with a condenser in the laboratory where the column would typically be on a reactor. Additionally, fluids can pool in plant configurations (**Figure 3**), for example distillation heads, reflux dividers, on column packing or even in transfer lines, which cannot be emptied during operation.
- The chiller unit for a lab condenser will provide far more chilling capacity per unit volume of both coolant and vapour than a standard plant will use, which may also be shared with other units.
- Plant cooling may be reliant on a simpler heat exchange system, such as a cooling tower, rather than a laboratory oil/glycol-based unit, so plant coolant temperatures of <15°C may not be achievable, particularly in summer. Thus, relying on having highly effective condensing power in the lab (such as a dry ice-cooled solvent trap) will not give a realistic picture of likely condensing performance on scale up.

SUMMARY

Whilst the considerations outlined herein can usually be easily remedied with suitable engineering solutions, an awareness of the physical changes associated with scaling up will lead to a more plant-ready process. By taking a rational, informed approach to experimental techniques and choice of reagents and solvents, late-stage engineering changes and/or ad hoc chemistry optimisation can be avoided, saving both time and money and reducing the risk of failure when commencing commercial scale production.