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Review

Scalable Reactor Design for Pharmaceuticals and Fine Chemicals Production. 1: Potential Scale-up Obstacles

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Abstract:

A comprehensive review of factors that inhibit scalability of fine chemicals and pharmaceuticals, from the chemical engineering point of view, is presented. These potential scale-up obstacles are generated by the fact that chemical rate constants are scale-independent, whereas physical parameters and phenomena are not. The paper identifies the most common factors that interact with chemistry to cause a fall in performance on scale-up and suggests ways in which these issues can be analysed in order to generate appropriate solutions. A hierarchy of the importance of the potential scale-up obstacles as perceived in industry is presented based on information collected from chemical companies, while the merits of scale-out as opposed to scale-up are addressed.

Introduction

The process and development literature contains many accounts of reactions that have been scaled-up. Unfortunately many of these accounts are often cast from a particular discipline standpoint and thus miss discussion of elements of the scale-up that would be critical components of a discussion from another scientist's perspective. The objective of this paper is to identify factors that may inhibit scalability. To do this we wish to categorise difficulties encountered in scale-up and see where and how these problems can be remedied.

There are a number of possible ways of examining the scale-up process within the overall drug development programme, differing in terms of the scope of the development process. This viewpoint will affect the selection of changes to the equipment or chemistry required in order to achieve a particular aim. In this paper, we will confine our view to that of the reaction engineering aspects dealing with process selectivity and yield optimisation. For the pharmaceutical industry there is another consideration of validation to think about. Process validation requires that the reaction is "well understood" and that the product can be maintained within quality control bounds for allowable variations in the processing conditions. This validation is undertaken to determine the effect that variations will have on the optimum production route. It is easy to see the link between process modelling and process validation, although the latter is normally a final consideration in process development.

Whilst it is immediately obvious that multiphase reactions are inherently more difficult to scale-up, there are still obstacles and difficulties encountered in the scale-up of "standard" single-phase reactions, and these difficulties are also present in the more complex multiphase reactions. The discussion will be initially focused on problems inherent in the scale-up of homogeneous reactions. Later sections will develop the issues associated with multiphase reactions.

Review of Current Scale-Up Obstacles

First it is necessary to discuss what is meant by scale-up and the type of issues found during scale-up of a reaction process. These can be divided into operational, modelling, and management due to their impact in the relevant area. Paul gives a useful description of what is a successful scale-up.[1] "Successful scale-up can be defined as plant operation that achieves the same conversion, selectivity, and product distribution as defined in the laboratory". From our point of view, this is extended to *the capability to predict and verify optimum performance criteria*, implying both an ability to model accurately any particular scale and an ability to optimise the reaction system that is modelled. The difficulties experienced with scale-up can be divided into those associated with intrinsic chemical issues and those associated with the physical environment in which the reaction is carried out. In the former belong issues associated with handling of dangerous substances. For example, Control of Major Accident Hazard regulations (COMAH) imposes regulations on storage and use of hazardous materials,[2] which are dependent on scale. Even though not discussed in this paper, it must be recognised that Health and Safety issues and Risk Assessment aspects are part of a wide subject with a strong impact on the scale-up of any chemical process.

The difficulties associated with scale-up can be largely categorised into two types of problems. The first is one where the reaction system requires a complex physical operation

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on a large scale that is unworkable compared to the "simple" operation on a small scale. An example of this sort of problem would be semicontinuous powder addition. It is not difficult to periodically add small quantities (e.g., spatula loads) of $AlCl_3$ to a reaction in a fumehood, but it is impractical on the large scale due to the difficulties in handling this material (a hygroscopic powder which generates HCl on contact with water). A preferred scale-up method would look at reversing the addition and adding reagents to the whole aliquot of the $AlCl_3$. This then is an **operational** issue, in the sense that the action required and performance obtained depend on the scale of operation. For either addition procedure the chemistry could be modelled and the reaction outcome predicted.

A second type of problem is that associated with measuring or modelling a process variable. Whilst the physical scale-up may not be difficult, the alteration in scale may change an unmeasured critical process parameter or may tip the trans balance of two competing pathways for the reaction. If the understanding of the reaction is only that of a statistical probability of the outcome on a small scale, it has no validity for extrapolation, and if for whatever reason the critical process variable is not assessed then any prediction is fraught with uncertainty. For example in catalytic hydrogenation, it would be desirable to measure the solution-phase concentration of hydrogen, but this is difficult and the headspace hydrogen pressure is often stipulated instead as a process parameter. The solution concentration is by implication taken to be the equilibrium concentration at that pressure, and the kinetics for the hydrogenation reaction is calculated accordingly. However, as Sun et al.[3] have shown, by affecting the solution-phase hydrogen concentration, the mass-transfer rate during the reaction can have a radical influence on the outcome of the reaction. It is not sufficient in this case to say that mass transfer was "adequate"; the total reaction model requires that the coupled mass transfer process is modelled in order to describe the total reaction process. This second type of scale-up issue is a **modelling** difficulty, due to either the complexity of obtaining accurate data (as in the case of hydrogen solution-phase concentration) or the mathematical complexity required for modelling of the additional outcome-critical process.

In 2002, recognising the need to eliminate the hesitancy to innovate, the U.S. Food and Drug Administration launched the initiative "Pharmaceutical CCGMP's for the 21-st Century: A Risk-Based Approach". As part of this initiative a comprehensive guidance for industry[4] underlines the necessity and the benefits for early understanding of a new process. According to Process Analytical Technology (PAT) guidance[5,6] a process is generally considered well understood when (1) all critical sources of variability are identified and explained; (2) variability is managed by the process; and (3) product quality attributes can be accurately and reliably predicted over the design space established for materials used, process parameters, manufacturing, environmental, and other conditions. To achieve a good understanding of the process, multivariable mathematical approaches for design, data acquisition and analysis such as statistical design of experiments, response surface methodologies, and process simulation and pattern recognition tools as well as suitable process analysis and control tools are recommended. BRITEST[7] employs various tools which analyse a process and show how major improvements might be possible. An increased appreciation of the value of collecting process data during production has driven the development of various modern process analysis tools. Types of measurements include at-line, where the sample is removed, isolated from, and analyzed in close proximity to the process stream; on-line, where the sample is diverted from the manufacturing process and may be returned to the process stream; and in-line, where the sample is not removed from the process stream and can be invasive or noninvasive (e.g., Raman spectroscopy through a window).

Some existing limitations to scale-up are revealed by reviews of safety incidents. Those involving operational breakdowns and accidents, and their underlying causes, are illustrative.[8,9] Etchells classified the first underlying cause in these incidents as a *poor understanding of the reaction chemistry or kinetics*.[8] This was further qualified into the following:

(a) underestimation of the heat evolved;

(b) unanticipated side reactions, including formation of unstable byproducts;

(c) changes in onset temperature (for decomposition or runaway);

(d) unpredicted autocatalysis.

Other underlying causes of incidents can be associated with the plant design such as insufficient mixing and cooling of reaction mixtures or poor plant modelling (especially heat transfer limitations, dead times, and other thermal lags). Some of these incidents could well have been avoided if small-scale investigation had been performed under the appropriate conditions to match those found in the larger plant. This raises the question of how do we determine what experiments are required on a small scale in order to predict large-scale performance? An example of a reactor exploding after cooling (not heating) of an incorrectly neutralised nitration reaction mixture is discussed by Gustin:[10] cooling allowed an unstable nitrophenate species to crystallise on the walls of the reactor. This illustrates the difficulty in foreseeing what experiments should be conducted to test for process safety and the related scale-up problems.

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(5) Process Analytical Technology on website of American Association of Pharmaceutical Scientists, www.aapspharmaceutica.com/inside/focus_groups/PAT/index.asp.

(6) Process Analytical Technology, www.processanalyticaltechnology.com

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Further underlying causes of under-rated control and safety backup systems are arguably part of the detailed plant design rather than the scale-up design itself (although clearly related). Underlying causes associated with inadequate procedures and training have less relevance to the issues associated with difficulty of scale-up but should not be dismissed altogether due to their implication for the level of complexity of plant design.

These scale-up related safety incidents are examples after the fact, but not all cases of poor scale-up will lead to hazardous incidents and often the root cause of the incident where poor scale-up methodology is involved has other management aspects as a factor. These **management** issues will largely not be dealt with in this study, although they are clearly related to the ability to reliably predict the scale-up outcome.

In general then problems may be encountered where the relationship between intrinsic kinetics and external physical parameters is not held constant during the scale-up. Atherton[11] states the following:

These problems are commonly caused by the interaction of the chemistry of the process with physical variables, and this is an area where the chemist should be well placed to identify and anticipate difficulty. There is an important principle involved which I have not seen stated explicitly elsewhere, but which I regard as axiomatic, namely: **chemical rate constants are scale independent, whereas physical parameters are not**. *This dichotomy is the primary cause of the failure to identify scale-up problems*.

He further identifies a list of factors “which most commonly interact with chemistry to cause a fall in performance on scale-up” to include processing time, heat transfer, power input, gas desorption, phase separation, mixing times, and mass transfer rates in two-phase systems. This study will examine these and other effects in turn and suggest ways in which these issues can be analysed and appropriate remedies can be found for standard reaction configurations.

Single-Phase Reactions

1. Lack of Knowledge of Physicochemical Properties: (Management). To give a consistent viewpoint for this task, a standpoint will be taken of an engineer attempting to check scale-up feasibility. This assumes that the issues to do with availability of reagents and safety measures for working with these reagents are already known and have been successfully addressed in the laboratory. It also assumes that the physical properties of the product and intermediate compounds are known or can be measured from available material. *This basis for the scale-up is in fact the first obstacle for scale-up*, in that if suitable information is not available then the scientists charged with process scale-up will make broad assumptions, and the reliability of the scale-up process itself becomes subject to more risk. There is obviously a tradeoff between spending time conducting experiments to evaluate parameters required for the reactions to be scaled-up and conducting large-scale trials in order to determine the actual outcome. The use of large batch reactors has been a product of the normal approach to handling process uncertainty. With these systems it is simple to leave a reaction running for longer or add a little more reagent to rectify a difficulty caused by the uncertain behaviour of a reaction. The down-side of this approach is that it allows a sloppy attitude to scale-up with the emphasis on obtaining product at the cost of information such as the physical parameters and properties that will allow for a better reactor design. This information is intrinsically valuable to a development process, as it may allow for a better designed reaction system which will avoid the scale-up difficulties that traditional methods are poorly suited to handle.

2. Material Transfer Time: (Operational). Filling times for large-inventory equipment can be significant.[12] A simple example of this is the time required to fill a 10 000 L reactor via a 40 mm diameter feed pipe. If the exit velocity is restricted to 2 ms^{-1} (in order to reduce splash, gas entrainment, or static generation), then the time taken to fill the vessel will be greater than 1 h. For some low-dielectric-constant solvents, such as toluene, working superficial velocities in the transfer piping may be restricted to 1 ms^{-1} in order to reduce possible static generation.[13] The arrangement of piping, the pipe materials of construction, bonding, and the grounding of the pipework also need to be considered in order to reduce this static buildup.

Because some construction techniques such as welding and cutting may require a complete plant shutdown, then the obvious remedy for slow transfers of replacement of narrow-bore tubing with larger-bore sections requires careful consideration. The additional line inventory and flange area come into consideration also. The physical design of specialist “flexible” pilot equipment may already have built-in connections unnecessary for the process at hand. This in turn could give dead space volumes that would not occur in a bespoke design. These equipment design issues are largely outside of the idealised scale-up problem but still intrude due to their unexpected consequences on operation of the pilot plant chemistry.

To reduce the volatile organic vapour discharges from a plant, it is common practice to not transfer volatile solvents under a live vacuum. This leaves the possibility of using a dead vacuum transfer technique, where the vessel is first evacuated, then isolated, and then the solvent is introduced under the residual vacuum. This is not suitable for those solvents with a high vapour pressure, as flashing will occur. For low-viscosity solvents, the use of uncontrolled vacuum transfer could also lead to excessive pipe velocities. Solvent transfer via a pump can lead to difficulties with cavitation and contamination, as well as the possible hazard of seal failure. The simplest solution for liquid transfer is either gravity feed or blowing the liquid into the vessel. Typically

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only very low positive pressures can be used due to thin-wall storage drums and the danger of overpressure. A double handling of the liquid solvents is often used in order to allow a final quality check on particulate and other contamination prior to their charging from storage to a header tank and then to the reaction vessel.[14] Due to the use of statistical sampling for inspection of inward goods, not all of the solvent drums may have been sampled. The step of charging to a header vessel allows for a final inspection and filtering, catching any heterogeneous contaminants prior to their inclusion in the reaction mass.

The handling of pyrophoric liquids is particularly difficult. Safety is the paramount concern, and active blanketing of the charge vessel and receiving vessel is necessary in order to prevent reaction with air or water vapour. Commonly encountered examples of these materials are BuLi solutions and some solutions of hydride reagents such as DIBAL.[15] Related to this is the safety issue of how quickly can the contents be transported for further processing or be dumped into a quench system if required.[10] Longer residence times are not unusual in pilot plant and production work where materials may be held in transfer vessels and lines for many days, possibly at ambient temperatures. This is quite different to common laboratory practice where products are comparatively rapidly isolated, purified, and rapidly cooled in storage until required for later reaction. The investigation of the reaction in the laboratory therefore needs to take into account the potentially lower addition rates due to transfer limitation available on scale-up.

3. Heat Transfer Time: (Operational, Modelling). Lower rates of heat-up and cool-down of large batches can cause problems if there is a possibility of reagent or product thermal decomposition during this extended period. Many instances are known where the speed of a reagent addition step is determined by the ability of a reactor to control an exothermic semibatch reaction process.[16−18] The longer time for the high-temperature reaction step may then have implications on product selectivity.[19,20]

Table 1. **Values for the parameters in eq 2 as function of agitator employed**

stirrer	K	a	
anchor	1	0.5	for $10 < Re < 300$
	0.36	0.67	for $300 < Re < 40\,000$
pitch-bladed turbine	0.44	0.67	
flat-bladed turbine	0.76	0.67	

Modelling and parameter estimation for the heat-transfer coefficient can be a critical feature of the scale-up in these situations.[21] The evaluation of process fluid, vessel wall, and service fluid contributions to the overall heat transfer coefficients is possible by careful experimentation using techniques such as the Wilson method for determining film coefficients.[22] This method enables accurate values to be calculated for the heat transfer coefficients for working reactor systems. The overall heat transfer coefficient, U, can then be readily obtained from (1). Correlations such as (2) have been used for "standard" geometry mixing vessels, so that similar behaviour should be expected from real production-style reactors. Values of K and a for this correlation are given in Table 1.

$$\frac{1}{U} = \frac{1}{h_r} + \frac{d_w}{\lambda} + \frac{1}{h_j} \tag{1}$$

$$\frac{h_r d_r}{\lambda} = K Re^a Pr^{1/3}\left(\frac{\mu}{\mu_W}\right)^{0.18} \tag{2}$$

With a good knowledge of the individual and overall heat-transfer coefficients, the surface contact temperatures can then be estimated assuming pseudo-steady-state conduction. For the case of a less than full vessel, the likelihood of splashing onto local hot or cold jacket areas is high, and this may affect product decomposition or crystallisation events, so that the effect of contact temperatures in the main swept area and the possible extremes should be considered.

It is well-understood that the surface area per unit volume decreases as the vessel size increases. For the common style of a glass-lined jacketed reactor, the specific area for heat transfer is also a function of the percent vessel loading, as a lot of the proportion of heat transfer area is located at the bottom of the vessel.

4. Process Control: (Operational, Modelling, Management). The development of control systems and control parameters for the safe operation of batch reactors is a study in its own right. The use of batch reactors is common in the pharmaceutical industry, as they are supposedly more flexible for the types of reaction system that can be tackled.[23] The difficulty in using a batch reactor is the inherent control problem with a large inventory of material which is undergo-

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ing a dynamic (reaction) process.[24] This is exacerbated if the reaction is catalytic or autocatalytic due to the potential change of reaction rate, and hence heat release rate. Obviously the degree of safety programmed into the control system needs to be higher as the hazard (i.e., inventory) is increased, but a more complex control strategy requires that there is adequate management of the human element associated with reactor operation.

5. Mixing Time: (Operational, Modelling). Changes in the selectivity of a reaction can be categorised into macro-, meso-, and micromixing issues depending on the time scale of the reaction process.[12] Macromixing relates to the time scale of bulk homogenisation. In the extreme case, bulk mixing may be so poor as to result in a mixed and an unmixed zone in the same reactor (infinite mixing time), with potential dire consequences.[11] Mesomixing relates to the dispersal and disintegration of reagent plumes; the localised excess concentration that can result can have a great effect on conversion and product distributions. On a more rapid time scale is micromixing which is mixing (by molecular diffusion or fluid engulfment) on the smallest scale of motion also known as the Kolmogoroff scale, where, even in a highly turbulent fluid (with strong velocity fluctuations), the flow is no longer turbulent but laminar. Depending on the reaction time scale (e.g., a short reaction half-life) the product distribution could be affected by changes due to micro-, meso-, or macromixing on scale-up.[25−28] Whereas macromixing is concerned with the blending time for the whole solution and is of the order of seconds to minutes, meso- and micromixing time scales are of the order of milliseconds.[25]

An example[11,28] of neutralisation of an acidified solution of ethyl chloroacetate illustrates this concept:

$$OH^- + H^+ + ClCH_2CO_2Et \xrightarrow{k_{Primary}} H_2O + ClCH_2CO_2Et$$

$$OH^- + ClCH_2CO_2Et \xrightarrow{k_{Secondary}} ClCH_2CO_2{}^- + EtOH$$

In this case both the primary (desired) reaction and secondary (undesired) reaction are both relatively fast second-order chemical reactions, but the primary reaction's rate is of the order of 10^{10} times faster. If a stoichiometric amount of base is added to the reaction vessel, then, without consideration of the mixing process, it is expected that only the primary reaction would occur since its rate constant is so much greater. The mixing process is important in this case as there is a localised excess of the hydroxide in the dispersing reagent plume, which then gives rise to the secondary reaction. The time scale for the secondary reaction is of the order of the eddy dispersal time (milliseconds). The magnitude of this undesired second reaction depends on the time taken for dispersal of the localised excess of the feed plume compared to the characteristic time for the reaction. Thus a slow addition of base to a cold solution should decrease the plume dispersal time and increase the hydrolysis time. This secondary reaction is not as fast or extensive as the primary diffusion-controlled reaction but is occurring in a smaller localised region than the bulk mixing process, hence the use of the term meso-mixing for the plume-dispersal related mixing.

A similar potential mesomixing dependence was observed for the gas evolution from a Boc group removal.[29] The reaction required 2 equiv of acid; the first being consumed in amine neutralisation, with the second equivalent generating gaseous butene and CO_2 via an acid-catalysed elimination and decarboxylation mechanism. On a small scale this stepwise process was observed, but on scale-up the gas evolution preceded the addition of the second equivalent of acid presumably due to a mesomixing effect of the strong acid plume with the surrounding solution.

These mixing effects are instances of the inability to replicate on a larger scale the nature of the "ideal" reaction conditions used on a small scale. The converse can also hold, as discussed by Paul,[1] for a hydrolysis reaction. The reactant needed to be extracted from an organic phase into an aqueous phase to be hydrolyzed and separated from forming impurities. An industrial centrifugal extractor could provide rapid contact of the reacting phases due to a high interfacial area, an optimal residence time to perform the hydrolysis and at the same time to avoid product decomposition. Since a small scale extractor could not reproduce such performance, the reactive extractor used in the scaled-up plant could not be scaled-down successfully to the bench scale for testing. Thus, the production version was designed "in the absence of an integrated laboratory model" and gave a greater conversion than the original bench-scale reaction system. Although this is a two-phase example it illustrates the point.

Bulk blending times in stirred tanks have been found to be of the order of 3−5 times the circulation time. For systems above the critical impeller Reynolds number, Re_c, the mixing time can be estimated via a correlation using the Fourier number:[12]

$$Re_c = 6370 Po^{-1/3} \tag{3}$$

$$Po^{1/3}\, Re Fo = 5.2, \text{ provided } Re > Re_c \tag{4}$$

An example would be an aqueous solution in a tank mixed with a four-bladed 45° turbine of 92 cm diameter ($Po = 1.5$) running at 90 rpm in a 1.83 m diameter tank (Pfaudler RA72-750). For this case $Re = 1.3 \times 10^6$, $Re_c = 5600$, and $Re \gg Re_c$. The Fourier number is found to be: $Fo = 3.6 \times 10^{-6}$, and thus the bulk mixing time t_m is estimated as 12 s (total mixing power of 3.3 kW). A 50% increase in the

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mixing speed decreases the mixing time t_m to 8 s, but the power requirement is now 11 kW, which is beyond the capability of the standard motor fitted of 7.5 kW. This correlation has been developed for the mixing of fluids of similar densities and viscosities and should be used with care, as greater mixing times could result in practice when mixing dissimilar fluids.

From the Kolmogoroff microscale used in the analysis of turbulent eddy dissipation, the lifetime of an eddy can be related to the kinematic viscosity, ν, and the energy dissipation rate per kilogram of fluid, ϵ:

$$\tau_K = 12\sqrt{\frac{\nu}{\epsilon}} \tag{5}$$

From this, the rate of engulfment can be used to describe the increase of the reaction zone in a semibatch reactor, where the major reaction zone is close to the addition point and the bulk contents of the vessel are playing little part in the reaction. The lifetime associated with this engulfment rate, τ_E, is

$$\tau_E = \frac{\tau_K}{\ln 2} = 17.3\sqrt{\frac{\nu}{\epsilon}}, \tag{6}$$

This is the time constant of micromixing by engulfment, which determines the micromixing rate of low to medium molecular weight solutes in common low viscosity liquids.[25] A comparison of the lifetimes of the secondary reaction processes and lifetimes for mixing and addition is now possible. Care needs to be taken to check that an appropriate value of the energy dissipation rate is used, as this can vary by 1 order of magnitude above and below the mean value for different choices of inlet pipe location.

For the example used above, if the vessel contained 2000 L of aqueous material, then, with a total power consumption of 3.3 kW, this would give an average energy dissipation rate of 1.7 W kg^{-1}, but it could vary from 0.5 W kg^{-1} at the liquid surface to 25 W kg^{-1} close to the agitator shaft (these numbers are illustrative only). In critical situations, computational fluid dynamics (CFD) could be used to model the energy dissipation rates for a given vessel and impeller geometry. Taking the lower figure of 0.5 W kg^{-1} as an example, this would give about 25 ms for the engulfment lifetime. If a secondary reaction process (using local feed stream concentrations) has a similarly short lifetime, then the mixing of the feed stream into the bulk solution will affect the product distribution. If the feed point was shifted closer to the agitator, a potential reduction of the engulfment time scale to 3.5 ms is possible, and hence a consequential alteration to the product selectivity.

If the reaction time scale τ_R for the primary reaction is of the order of t_m, then the primary reaction will be localised in one part of the vessel and the exo- or endotherm generation will be localised with it. This has implications for heat transfer models and raises the possibility of localised transient temperature gradients in the larger vessel. This localised heating could lead to local vaporisation in an extreme case. This has been found to be possible even where the bulk enthalpy-concentration conditions are below the boiling point curve, but during the mixing process the mixture can exceed the local boiling point.[30]

If τ_R for the secondary reaction is of the order between t_m and τ_E, then the addition of reagent to the vessel will need to be carefully conducted and adequately modelled to ensure similarity of outcomes on scale-up.[23] At an intermediate level of analysis the use of 2-D and 3-D networks of zones to simulate the effect on reaction of mixing has given some useful results.[31,32] This approach allows simulation of mixing effects in reaction processes taking into account crude results obtained from CFD results or other observations for pure mixing and turbulence interactions.

A different approach to the problems of mixing and reaction is offered by microchannel mixers.[33−35] Due to the absence of turbulence in microfluidic devices, mixing relies on molecular interdiffusion and chaotic advection. Its enhanced performance derives from maximization of interfacial surface area and concentration gradients due to small channel dimensions (order of hundreds of micrometers). Two basic principles are followed to induce mixing at microscale, according to what type of energy source is utilised to drive the mixing process. The so-called “active mixing” utilises external energy sources such as ultrasound, acoustic, bubble-induced vibrations, electrokinetic instabilities, piezoelectrically vibrating membrane, etc. “Passive mixing” uses the flow energy, e.g., due to the pumping action or hydrostatic potential, to restructure a flow in a way which results in faster mixing. This is achieved by various methods such as thin multilamination of unmixed reactants feed, split-and-recombine flow guidance, and injection of many streams (e.g., via nozzles) into one stream, where the collision of jets provides a means for fast mixing. Nowadays, there is a wide range of micromixers commercially available[36,37] which have flows from sub-mL/h to 10 m^3/h covering a wide range (up to the conventional static mixers), being amendable to chemical synthesis and chemical production as well. The use of micromixers in chemical synthesis brings several advantages, especially when fast reactions are involved. Due to short mixing times and well defined mixing behaviour, as well as narrow residence time distribution, byproduct formation can be minimised and increased yield and selectivity can be achieved.[38,39] For example, by replacing the traditional batch phenyl boronic acid production with a continuous flow

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(34) Nguyen, N. T.; Wu, Z. Micromixers − a review. *J. Micromech. Microeng.* **2005**, *15*, R1−R16.

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(36) Ehrfeld, W.; Golbig, K.; Hessel, V.; Löwe, H.; Richter, T. Characterisation of mixing in micromixers by a test reaction: Single mixing units and mixer arrays. *Ind. Eng. Chem. Res.* **1999**, *38*, 1075−1082.

(37) Hessel, V.; Löwe, H.; Müller, A.; Kolb, G. *Chemical Micro Process Engineering, Processing and Plants*; Wiley-VCH: Weinheim, 2005.

(38) Wörz, O.; Jäckel, K. P.; Richter, T.; Wolf, A. Microreactors, a new efficient tool for optimum reactor design. *Chem. Eng. Sci.* **2001**, *56*, 1029−1033.

process that uses a micromixer/tubular reactor, an increase in yield by 25% is reported due to reduction of side/consecutive products.[40] The side and consecutive products are reduced to levels below 1%, thereby increasing selectivity and facilitating separation by elimination of a distillation step.

6. Contact/Residence Time: (Modelling). The relationships among the conversion, the inherent kinetics for the reaction, and the reactor configuration are expressed in design equations relating residence times, conversions, and reaction rates. As an example, the design equation for a constant-volume plug-flow reactor (as well as a constant-volume batch reactor) is given by eq 7.

$$\tau = \frac{V_L}{\upsilon_0} = c_{A0} \int \frac{1}{-r_A} \mathrm{d}X_A \tag{7}$$

The design equation expresses the central point of the scale-up, where many of the parameter values are kept constant or are varied intentionally with the system volume. Difficulties with this simple idea can come from a number of places including the inability of a simple plug-flow or efficient backmixing to describe the true hydrodynamic situation (and this altering as a function of scale) and complications of nonhomogeneous reaction kinetics. Problems such as bypassing in a CSTR, or dead volumes in a large reactor, can be assessed by determining the residence time distributions for continuous flow equipment, but added complexity is required in order to scale-up successfully.

Roberge et al.[41] classified the reactions in the fine chemical and pharmaceutical industry according to reaction half-life time, $t_{1/2}$, as follows: fast for $t_{1/2} < 1$ s, rapid for 1 s $< t_{1/2} <$ 10 min, and slow for $t_{1/2} >$ 10 min. The latter suit batch processes, but a continuous process would bring a safety or quality advantage, if short exposure to high temperature and pressure is required, since this can be difficult to achieve in batch operation. Fast reactions (e.g., reactions that involve reactive species such as chlorine, bromide, amines, organometallics, and reactions that are often performed at subambient temperature) are very sensitive to mixing and are particularly suitable for micromixer/microreactor systems. Furthermore, a microreactor system would be beneficial in order to provide a better control of heat flow and reaction temperature.

7. Plant Limitations: (Operational). The ability to handle the issues of physical containment of the reaction system plays a part in decisions made during scale-up. This can be anything from mixture swelling, frothing, or flooding[42] through to more standard considerations of corrosion and consequent product contamination.

The pressure, vacuum, and maximum and minimum temperature ratings of "standard equipment" are considered as a part of the scale-up. Often these parameters of a reaction are targeted in order to improve the "plant fit".[43,44] Some of these limitations can be compounded due to plant service limitations and hence avoided with a bit of creative thinking. For example the use of direct liquid nitrogen cooling in reaction systems via semiadiabatic operation is a relatively recent advance allowing standard glass-on-steel vessels to work at lower temperatures.[45]

Multiphase Reactions

So far the discussion has concentrated on single-phase systems. However, the conclusions are equally applicable to multiphase reactors. When the reaction system has more than one phase, additional scale-up obstacles are associated with mass transport, suspension, and phase continuity. The coupling of the requisite transport processes with chemical reaction necessarily complicates scale-up. Both failure to maintain interfacial area per unit volume for liquid phases and failure to maintain reactive surface area in solid-supported reactions are common occurrences in scale-up. In brief the difficulties relate to particle transport, mass transfer, interfacial area, emulsion formation and stability, and phase continuity−phase inversion.

Solid−Liquid Systems

8. Solid Addition: (Operational). Continuous solid addition to a process is a rarity in the pharmaceutical industry. This is largely due to the difficulty in handling continuous control and the difficulty of hopper design and management. Periodic addition of solids by operators is customary but obviously labour-intensive and prone to incidents of safety hazard (dust, splash) and also introduces process variability from small timing changes and practical charging rates when handling large quantities of materials.[23] The best approach arguably is to avoid solids addition and either start with solids charged to a vessel and then add solvent and other reagents or add stable slurries or concentrated solutions rather than the solids themselves.

9. Solid Suspension: (Operational, Modelling). Suspension of solids ranges through a number of descriptions for the mixture. As the agitation is increased the degree of suspension can be categorised by (in increasing order of power required) the following:

(a) near-complete suspension (with some of the solids stationary);

(b) complete particle motion;

(c) just suspended (complete off-bottom criteria);

(d) uniform suspension.

For solid suspension in well-controlled chemical reactions, the desired criterion is at least "complete particle motion".

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(39) Yoshida, J.; Nagaki, A.; Iwasaki, T.; Suga, S. Enhancement of chemical selectivity by microreactors. *Chem. Eng. Technol.* **2005**, *28*, 259−266.

(40) Hessel, V.; Hofmann, C.; Löwe, H.; Meudt, A.; Scherer, S.; Schönfeld, F.; Werner B. Selectivity gains and energy savings for industrial phenyl boronic acid process using micromixer/tubular reactors. *Org. Process Res. Dev.* **2004**, *8*, 511−523.

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(42) Stoessel, F.; Fierz, H.; Lerena, P.; Killé, G. Recent developments in the assessment of thermal risks of chemical processes. *Org. Process Res. Dev.* **1997**, *1*, 428−434.

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(44) Borland, J. N. Speciality Chemical Manufacturing in the UK, Has it a Future? In *Pilot Plants and Scale-up of Chemical Processes II*; Hoyle, W., Ed.; Royal Society of Chemistry: Cambridge, 1999.

(45) Powell, L. Plant-scale reaction down to −100 °C. In *Pilot Plants and Scale-up of Chemical Processes*; Hoyle, W., Ed.; Royal Society of Chemistry: Cambridge, 1997.

This will avoid buildup of fillets of solid material in the less turbulent spaces in the reactor, which could lead to caking of the reagent and compromising the reaction. More preferable is a criterion of just suspended particles where all the solid particles are transported throughout the liquid at a rate sufficient to obtain near-median mass-transfer, and are only in contact with the vessel bottom for a few seconds at most. Uniform suspension is required for paint and pigment purposes but is said to achieve little increase in mass-transfer effects over that obtained for complete off-bottom suspension.

Zwietering's correlation for the critical stirrer speed for complete off-bottom suspension, n_{JS}, is[46]

$$n_{JS}{d_a}^{0.85} = S\nu^{0.1}{d_p}^{0.2}\left(\frac{g\Delta\rho}{\rho}\right)^{0.45}X^{0.13} \tag{8}$$

This equation applies for approximately isodimensional particles. Care should be exercised for broad particle size distributions. S is a constant related to the impeller type, size, and location and vessel geometry[46] (see Table 2).

As the viscosity increases, it is more difficult for the turbulent eddies to sweep all the surfaces of the vessel with sufficient power to achieve suspension. This correlation also shows that on scale-up the stirrer speed can be allowed to decrease almost proportionately with the vessel diameter for geometrically related vessels. The biggest effect is from the ratio of relative density difference, implying that suspension of very dense particles or a change in crystal form for a previously used material may cause problems with adequate suspension.

A criterion for assessing the difficulty of solid suspension is the settling velocity. Solids with a settling velocity less than 5 mm s^{-1} represent an easy suspension problem and, if greater than 30 mm s^{-1}, a difficult one.[47] The settling velocity can be calculated for simple material geometries using an iterative process to estimate the drag coefficients. A conservative approach would be to use Newton's law:

$$u_t = 1.75\sqrt{\frac{gd_p\Delta\rho}{\rho}},\ 1000 < Re_p < 200\,000 \tag{9}$$

Equation 9 applies for $1000 < Re_p < 200\,000$ and predicts higher settling velocities than actually is the case for lower Re_p cases where Stokes' law can be used:

$$u_t = \frac{g{d_p}^2\Delta\rho}{18\mu} \qquad Re_p < 1 \tag{10}$$

For intermediate cases of Re_p the process to calculate the settling velocity is iterative and requires assessment of the drag coefficient from a chart. The true settling velocity in the intermediate Re_p range is lower than that determined by either of these two calculations.

10. Solids Dissolution: (Operational, Modelling). The modelling of reactive processes involving dissolution requires the use of a dynamic mass balance where there are terms for input to the solution phase due to mass transfer from dissolving solids and removal from the liquid phase due to reaction. As described, the following example is referring to a dissolving reagent, but equally a solubility-limited product could be tackled. For a dissolving solid, the molar input mass balance to a solution would have a term

Table 2. **Values for constant *S* in Zwietering's correlation, eq 8**

impeller type	d_t/d_a	d_t/C	S
six-blade turbine ($Po = 6.2$)	3	4	7.5
two-blade paddle ($Po = 2.5$)	2	4	4.8
three-blade propeller ($Po = 0.5$)	4	4	8.5

$$+ka_pV(C_i - C_\infty), \tag{11}$$

whilst the same mass balance could have for example a reaction term

$$-\nu k_r C_\infty^n \tag{12}$$

If the rate of dissolution is slow compared to the reaction rate, then the reaction process will be limited by the mass transfer process and a detailed description of the factors governing the mass-transfer coefficient and specific particle area will be required. Normally the interface concentration can be approximated with some limiting value such as the equilibrium solubility.

A standard approach is to look at the mass transfer occurring at the just-suspended condition. Until this point both the available surface area and mass-transfer coefficient will be increasing as agitation is increased, but from that point on only a small increase in the mass-transfer coefficient is found for most agitation situations.

The general form of the equation relating to the mass-transfer coefficient is

$$Sh = 2 + B{Re_p}^{0.5}Sc^{0.33}, \tag{13}$$

where values for B are in the range 0.6 to 0.72 depending on the system.[46] For the just-suspended condition, the value of u in Re_p can be taken as u_t, and correction for the effect of the size of particle has been determined for particles up to 10 mm.[46]

For uniform particles dissolving in controlled conditions, a measurement of the average mass transfer coefficient, k, can be made from their dissolution time t_d. This appears to give reasonable results except in the case of very small particles ($d_p < 50\ \mu$m).

$$\bar{k} = \frac{3\rho}{t_d a_p(C_i - C_\infty)M} \tag{14}$$

The equation assumes that the solution properties are not changing during the dissolution process, which may alter the C_i value and complicate the analysis. The value k is the average mass transfer coefficient covering the whole dis-

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(46) Harnby, N., Edwards, M. F., Nienow, A. W., Eds. *Mixing in the Process Industries*, 2nd ed.; Butterworth−Heinemann: Oxford, 1992.

(47) Oldshue, J. Y. Suspending solids and dispersing gases in mixing vessel. *Ind. Eng. Chem.* **1969**, *61* (9), 79−89.

solution process (since k itself changes due to the diminishing particle size).

Gas−Liquid Systems

11. Foam Creation: (Operational). The situation for gas/liquid contacting is more complex as it concerns mixing and mass-transfer from a separate phase (intentional gas addition or gas generated from reaction). The prediction of bubble properties is not straightforward as the coalescence of bubbles is highly dependent on the chemical species present in the liquid phase, and even minor amounts of surface active materials can affect bubble properties. There may well be an order of magnitude difference in the bubble diameter for a coalescing compared to a noncoalescing system with similar equipment operation. To determine the bubble diameter under given conditions, experiments need to be performed. With that information as a basis, scale-up can be attempted; however, the effect of other changes to the system, especially chemical composition, need to be carefully examined. The level of accuracy available from current literature predictions is poor except for simple air/water or electrolyte systems.

For reactions that generate gaseous products, foam production and its collapse and control can be the rate-determining factor. In the case of a diazotisation with concurrent bromide addition and nitrogen production,[48] the poor solubility of the intermediate meant that the reaction had to be slowed to allow for foam breakdown. Several commercial surfactants had already been tried unsuccessfully. A solution to this problem was a drastic change to the solvent (water) properties by dilution with acetic acid. This had the effect of a change in interfacial surface properties and altered solubility of the intermediate. The reagent addition could then be speeded up until it finally became controlled by the ability to control the exotherm in the production vessel.

Nonchemical solutions exist for mechanically collapsing foam. These include rake foam breaking from an overhead rake attachment to the agitator or addition of large-diameter floating spheres for surface collapse of the foam due to the shearing action of the spheres' movement when the vessel is stirred. Both of these solutions are still "ambulance at the bottom of the cliff" solutions, and it is probably better to alter the chemistry or solution properties in order to avoid foam altogether and allow for a higher reaction rate.

12. Gas Bubble Coalescence: (Modelling). There are two counteracting factors involved as gases are introduced to an agitated vessel. As the degree of agitation is increased, the bubbles will progressively disperse through more of the vessel's volume, until they start to circulate in a pattern below the agitator. This just completely dispersed criterion is desired as it will allow the whole of the tank volume to be used for gas−liquid contact. At higher power inputs bulk recycle is possible, similar to the description of homogeneous operation in solid−liquid systems. Counteracting the effect of the agitator is the gas flow rate itself. As more gas is introduced below the agitator, the bulk gas flow will become more core flow and flooding of the agitator is possible leading to a falloff in the mixing power supplied to the solution. The mixing power and gas flow rates both have effects on the gas holdup and therefore the gas residence time in the vessel.

There may be more complex effects to consider when the reaction rate is appreciable. Similarly, gas bubble shrinkage or expansion effects due to large liquid heads may need to be considered. For a six-bladed turbine the gas flow number Fl can be correlated with the Froude number Fr at the flooding point for coalescing systems[12]

$$Fl = 30\left(\frac{d_a}{d_t}\right)^{3.5} Fr, \tag{15}$$

so that the system should not be designed to operate at higher gas flow rates or lower agitation rates than indicated by this correlation. The higher degree of agitation, which results in bubbles completely dispersed above and below the agitator, can be correlated by

$$Fl = 0.2\left(\frac{d_a}{d_t}\right)^{0.5} Fr^{0.5} \tag{16}$$

A general relationship between the specific area and volumetric holdup of the dispersed materials (gas, liquid, or solid) phase and the continuous phase is

$$a = \frac{6V_{fd}}{d_{32}(1 - V_{fd})} \tag{17}$$

13. Off-Gas Properties−Gas-Phase Mass Transfer: (Modelling). Many batch reactions can be conducted in a dead-head manner where the addition of more gas is simply to replace that already consumed in the reaction (e.g., hydrogenation in an autoclave). Where the reaction is producing a gas byproduct, this would be a potentially dangerous way to operate due to the pressure buildup. The properties of the gaseous byproduct may need to be carefully controlled. Carpenter[23] gives an example of a diazotisation reaction where HF is also produced and carried out of the CSTR system. The reactor system was in this case specifically designed with the controlled release rate of HF in mind so that adequate and efficient continuous scrubbing of the off-gas could be achieved. An alternative batch configuration could potentially give an intermittent HF production rate that the scrubber would be unable to handle.

For a reactor design where there is gas reactant both in and out (e.g., in bubble columns), the exit gas properties need to be carefully managed and the combined mass-transfer and chemical reaction need to be addressed. An example of this is the oxidation of organics using air. The off-gas vapour content and oxygen content need to be controlled to avoid potentially explosive mixtures. This problem is perhaps more relevant to the fine chemical industry as the pharmaceutical industry uses extensive blanketing and purging in order to control off-gas concentrations, but as scale increases, this is an issue that does not go away. To determine the amount of gas reactants being consumed in a vessel, the mass-transfer

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(48) Bunegar, M. J.; Dyer, U. C.; Green, A. P.; Gott, G. G.; Jaggs, C. M.; Lock, C. J.; Mead, B. J. V.; Spearing, W. R.; Tiffin, P. D.; Tremayne, N.; Woods, M. Production of (*R*)-2-bromo-5-phthalimidopentanoic acid via a diazotisation process from (*R*)-ornithine. *Org. Process Res. Dev.* **1998**, *2*, 334−336.

Table 3. **Value of *H* for gases at 25 °C**

	water [MPa mol^{-1} L]	benzene [MPa mol^{-1} L]
H_2	128	32.6
N_2	156	21.2
CO_2	3.0	1.0

properties of the gas bubble may need to be considered. The specific mass transfer rate per unit volume between a gas and liquid can be described by a two-film mass transfer model:

$$N = K_L a \Delta C_L \tag{18}$$

where ΔC_L is a mean concentration difference between the bulk fluid and gas phases. The use of a liquid-phase description implies that the bulk gas concentration has to be related to its equivalent liquid-phase concentration via Henry's law or a similar solubility relationship. The overall mass-transfer coefficient K_L is related to the individual phase mass-transfer terms via

$$\frac{1}{K_L} = \frac{1}{k_L} + \frac{1}{H \cdot k_G} \tag{19}$$

For sparingly soluble gases, the first term will dominate the overall mass-transfer coefficient (e.g., gases such as H_2, N_2, O_2 in polar solvents). As the gas solubility increases, H decreases and both phases' individual mass-transfer terms contribute to the overall term (e.g., gases such as CO_2 and NH_3 in polar solvents) (Table 3).

The individual mass transfer coefficients can be determined, but the difficulty in evaluating the specific bubble area has meant that correlations are often made for the combined group K_La. Not a lot of data are available for nonaqueous systems, and the suggestion of Middleton is to correlate experimental data using[46]

$$K_L a \propto \left(\frac{P_G}{V}\right)^{0.7} (v_s)^{0.3-0.6} \tag{20}$$

For air−water systems the proportionality constant has been measured at 1.2, using an exponent value of 0.6 for the superficial gas velocity. For more general use a lower exponential value of 0.3 is suggested. The effect of dissolved materials is to normally increase the combined K_La, as the decrease normally found with k_L is offset by a decrease in the bubble diameter and an increase in the gas holdup.

Methods for calculation of the combined K_La term include the direct calculation from a knowledge of everything else in a dynamic mass balance and calculation by a dynamic method of system perturbation and monitoring the system recovery.[49]

The mean concentration difference that is used for the specific rate of mass transfer is often referred to conditions before and after the equipment. This implies that the gas bubbles pass approximately in plug flow through the vessel. Where there is significant recycle of bubbles, a recycle ratio should be introduced to the analysis, thus,[46]

$$\Delta C_\mathrm{L} = \frac{(\Delta C_\mathrm{in} - \Delta C_\mathrm{out})}{\alpha + 1} \ln\left[\frac{\Delta C_\mathrm{in} + \alpha \Delta C_\mathrm{out}}{(\alpha + 1)\Delta C_\mathrm{out}}\right] \tag{21}$$

$$\alpha = \frac{\text{Volumetric flow of gas recycled into the agitator}}{\text{Volumetric flow of gas to the vessel}} \tag{22}$$

where "in" and "out" refer to the concentration driving force of the inlet and outlet, respectively. For systems such as simple bubble columns, the gas is in plug flow, and $\alpha \cong 0$, which gives rise to the standard log-mean driving force expression. Where recirculation becomes significant is for values of α of around 1; as α increases to large values, then ΔC_in becomes equal to ΔC_out and the gas holdup becomes critical.

Liquid−Liquid Systems

14. Multiphase Mixing: (Operational, Modelling). Correlations exist for the mixing intensity required for draw down and dispersion of a light phase into a heavy continuous phase and the converse. With standard geometry reactors,[12]

for light dispersed in heavy:

$$\epsilon = 6.138 \times 10^{-7} \rho_c{}^{0.66} \Delta\rho^{0.96} \mu_c{}^{-0.4} V_{fd}{}^{0.24} \tag{23}$$

for heavy dispersed in light:

$$\epsilon = 1.89 \times 10^{-3} \Delta\rho^{1.1} \mu_d{}^{0.21} V_{fd}{}^{0.36} \tag{24}$$

This process is essential for successfully conducting binary liquid phase-transfer catalysed (PTC) reactions and two-phase reactions which are common in organic chemistry (e.g., many alkylation reactions and the Schotten−Baumann reaction). Little reaction will occur until the second phase is drawn into the impeller, and as the degree of agitation is increased the reaction rate will increase until the second phase is fully dispersed. Except for intrinsically very slow reactions which are not affected by hydrodynamics, agitation will decrease droplet size, increasing surface area per volume and hence increasing reaction rate. The degree to which a particular mixture will remain dispersed without inversion of the continuous phase depends on the mixing intensity, materials, and the history of the mixture. Experiments are needed to determine the phase behaviour as a function of the mixing intensity and composition, and scale-up is possible using constant mixing intensity, ϵ.

15. Phase Inversion: (Operational, Modelling). Stop−start operation (e.g., for sampling) may result in phase separation and phase inversion and could have potentially disastrous consequences on the reaction rate if the reaction system changes from reaction in the continuous phase to reaction in the dispersed. Care therefore needs to be taken over the operation of these systems to prevent the unwanted coalescence and inversion. Consideration is needed of where, how, and for how long the system should be mixed.

16. Liquid Droplet Coalescence: (Operational, Modelling). Because of greater liquid depths in large inventory batch reactors, the problem of clear-layer formation and settling is proportionately bigger as phase separations are

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(49) Trambouze, P.; Van Landeghem, H.; Wauquier, J. P. *Chemical Reactors: Design, Engineering, Operation*; Gulf Publishing: Houston, TX, 1988.

scaled-up. Although this is a workup issue, it is worth considering as a part of the reaction scale-up and development problem.

17. Emulsion Formation (Operational, Modelling). Emulsion formation and breaking is just as much of an art on a large scale as on a small scale. Experiments should be conducted to adequately cover the bounds of component and solvent composition changes in order to foresee where these problems lie.[12,23]

Catalysed Reactions

18. Catalyst Formulation (Operational, Modelling, Management). Although this study has not considered the choices of chemicals used for a reaction, these being largely inherent in the process, there are still choices over the physical form for reagents (e.g., particle size). Where this has the biggest impact is in catalysed reactions as the reaction process is directly linked with the mass-transfer limitations of the catalyst's form. Hence, for the development (rather than the scale-up) the choice over particle size, effective diffusivity, etc. are critical to the efficiency of the catalyst and the economics of the process. How the catalyst deactivates and the lifetime of the catalyst are both related to the designed turnover number (TON) for the catalytic process. It is therefore worthwhile to reconsider the reactor selection and suitability for catalysed processes very carefully, as different physical forms of the same catalyst may be better suited to different reactor designs.[50,51] An example of this is in the choice of particle size for a batch heterogeneous hydrogenation, where very small particles are preferred in order to assist suspension. If the same chemistry was attempted in a packed bed loop reactor, then larger particles would be preferred to lower the bed pressure drop. The design of the reactor and scale-up then relate to the designed:

(a) efficiency;
(b) lifetime;
(c) mechanical strength;
(d) ease of separation;
(e) deactivation/poisoning process.

These issues are largely related to the chemical kinetics but are often changed by the scientist working through the scale-up process, independent of the chemical transformation that the catalyst is conducting. Whilst not a difficulty with scale-up, these issues with catalytic reactions are open for manipulation as a part of the scale-up process. To a certain extent this is similar to the choice available for the physical form for a reagent in order to alter the release rate of that reagent into the reacting mixture.

19. Autocatalysis (Management, Operational). Where there is a difficulty with catalysed reactions is in the inherent ability of a control system to counteract the effect of any unpredicted autocatalytic process. If the reaction system does start to "run-away", then an (auto)catalytic process control can often not be re-established until the reaction is quenched, through either depletion of the reacting chemicals or addition of another reagent to break the cycle. This relates mostly to the confidence in scale-up: that the reaction processes are fully understood and that the response of the control system is fast and effective. As the inventory of a process is increased in scale-up, these assumptions need to be reviewed as part of the hazard and operability studies. The use of continuous or semicontinuous flow reactors for conducting catalytic reactions can therefore be seen as a means of controlling the inventory of material present in the reaction to minimise the effect of runaway.

20. Catalyst Control/Stability: (Management, Operational). A similar argument applies for the selection of form of catalyst for a reaction, with liquid formulation being normally preferred for reasons of ease of addition. The difficulty is then transferred to finding compatible solvent systems or maintaining uniform suspensions for the catalyst system in order to ensure that too much catalyst is not added to the reaction vessel. New batches of catalyst need to be assessed against the designed activity to ensure that the reactor system can cope with any potentially greater reaction rates. On one hand catalysed reactions allow for high productivities with low amounts of reagents (i.e., catalysts), but this is balanced by the difficulty in control as a change in the small amount of these materials will have a proportionately large impact on the reaction rate.

Scalability of Different Reactor Types

This study has largely been considering scale-up difficulties from the perspective of the current reliance on large stirred-tank reactors as the production reactors. There are many reasons for the current situation, many of which are self-imposed by the industry for more or less valid reasons. From the point of view of suitability for scale-up, it is worthwhile considering how the batch or fed-batch reactor fairs for handling these identified difficulties. Table 4 shows the categories of scale-up difficulties and the suitability of these reactor configurations against the results for idealised continuous reactors such as a Heatric-type multiplate, microstructured reactor or a multiple rotating disk reactor. These continuous reactor types are characterised by low inventory, low residence time, high heat transfer capability, and varying ability to handle solids and high-viscosity fluids.

The tick or cross marks placed in Table 4 are obviously subjective, and the reasoning for individual entries could be debated from a number of perspectives. The major factor in assessing each individual case is if the issue would cause a difficulty on scale-up and how easily it could be catered for in the reactor configuration under examination.

Thus, for those reactions where little is known about the material or kinetic properties, a batch reactor is debatably better suited than a more complex continuous flow unit, as the material can be simply held for longer until the desired specification is reached. For some designs of continuous reactors a turndown of the flow rates to increase the residence time may have other consequences that are more difficult to assess without the missing physical data.

Where a double tick mark is awarded, the inherent design characteristics of the reactor have eliminated the issue. For example, the excellent heat-transfer capabilities of microplate

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(50) Rase, H. F. *Chemical Reactor Design for Process Plants*; John Wiley: New York, 1977.

(51) Froment, G. F.; Bischoff K. B. *Chemical Reactor Analysis and Design*; John Wiley: New York, 1990.

Table 4. **Comparison of batch and fed-batch reactors with continuous, scaled-out reactor configurations**

Problem:	Batch	Fed-batch	Continuous with scale-out
1. Lack of knowledge of physico-chemical properties	√	√	✗
2. Material transfer time	✗	√	√
3. Heat transfer time	✗	✗	√√
4. Process control	✗	✗	√√
5. Mixing	✗	✗	√
6. Contact/residence time	✗-√	✗-√	√
7. Plant temperature or pressure limitations	-	-	√
8. Solids addition	-	✗	✗
9. Solids suspension	√	√	✗— √
10. Solids dissolution	√	√	✗
11. Foam creation	-	✗	√
12. Gas bubble coalescence	-	✗	√
13. Gas-phase mass transfer	√	-	√√
14. Multiphase mixing	√	✗	√
15. Phase inversion	√	✗	√
16. Liquid droplet coalescence	-	✗	√
17. Emulsion formation	✗	✗	√
18. Catalyst formulation	√	√	√
19. Presence of autocatalysis	✗	√	√
20. Catalyst control	✗	-	√

reactors allow for exothermic reactions to be tackled and scaled-out with ease, so that a small change in the heat generation potential of the reaction would not cause a difficulty.

Whilst batch reactors are clearly more difficult to control, they are forgiving to some extent with process uncertainty. At early stages of development the true timing for a reaction may be unknown and variable dependent on factors outside of the individual reaction, such as intermediate purity changes. The ability of a batch reactor to eventually blend away inconsistencies and hold the complete batch contents until it reaches specification are attractive features. Their downside is the slowness of operation. The time taken to perform reactions on a large scale is commonly underestimated, and the hazard associated with large inventories of material should never be underestimated.

In contrast, more novel reactor designs can allow better-controlled operation and be designed specifically to handle some of these scale-up problems. Microreaction technology is expected to have a number of advantages for chemical production.[52,53] The high heat and mass-transfer rates possible in microfluidic systems allow reactions under more severe conditions with higher yields than those of conventional reactors. Processes which necessitate specific reaction conditions, e.g., fast mixing, an exact temperature control, or a fast heating or cooling, can benefit.[54] New reaction pathways considered as being too difficult for application in conventional macroscopic equipment, such as direct fluorination of aromatic compounds, could be pursued, since in case of failure only small amounts of chemicals would be released and could be easily contained. The presence of integrated sensor and control units allow a failed microreactor to be isolated and replaced, while the other, parallel units continue production. These inherent safety characteristics make production scale systems of multiple microreactors possible, enabling a distributed point-of-use synthesis of chemicals with storage and shipping limitations, such as highly reactive and toxic intermediates such as cyanides, peroxides, and azides. Microreactors exhibit easy modulation and numbering-up for industrial production. The same process developed in a microreactor can be used to produce pilot-plant quantities in identical quality. By using a continuous process instead of batch processing, microreactor systems can be used to synthesise kilogram or even tonne amounts, particularly in parallelized arrays.[55−57] However, the microreactor concept is not a panacea, and every reactor design needs to be carefully matched to the particular chemistry undertaken.

Hierarchy of Potential Scale-Up Obstacles

A questionnaire was sent to a number of companies involved in active pharmaceutical and fine chemicals scale-

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(52) Ehrfeld, W.; Hessel, V.; Löwe, H. *Microreactors: New Technology for Modern Chemistry*; Wiley-VCH: Weinheim, 2000.

(53) Charpentier, J. C. Process Intensification and Miniaturisation. *Chem. Eng. Technol*. **2005**, *28*, 255−258.

(54) Pennemann, H.; Hessel, V.; Löwe, H. Chemical microprocess technology − from laboratory-scale to production. *Chem. Eng. Sci.* **2004**, *59*, 4789−4794.

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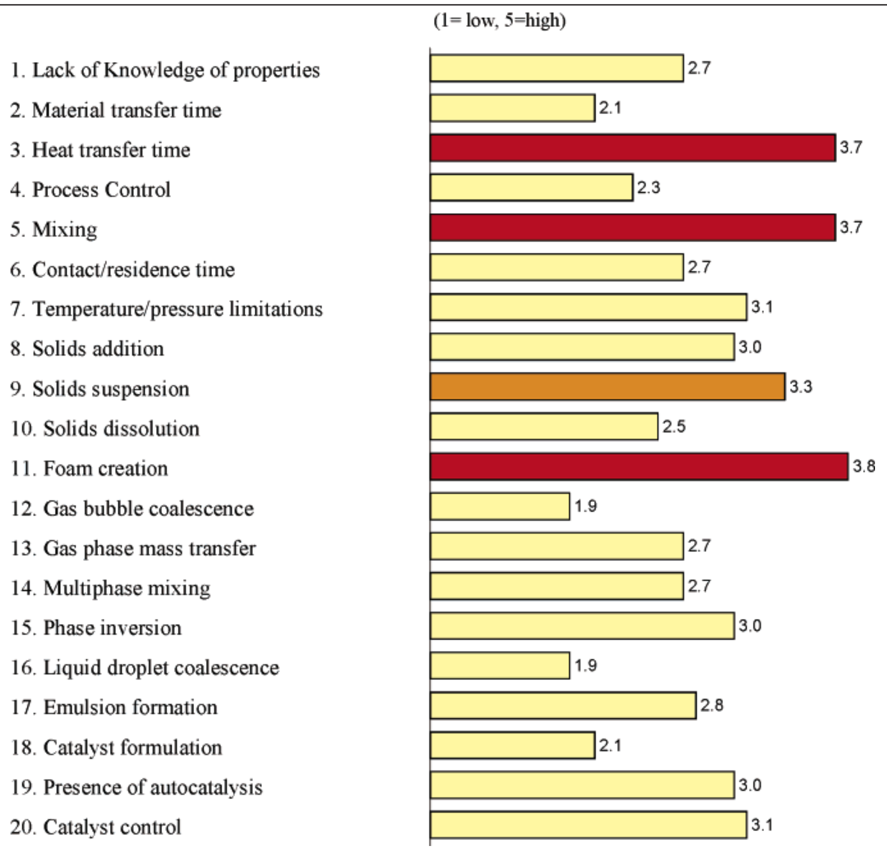
(56) Gavriilidis, A.; Angeli, P.; Cao, E.; Yeong, K. K.; Wan Y. S. S. Technology and applications of microengineered reactors. *Chem. Eng. Res. Des.* **2002**, *80*, 3−30.

(57) Jensen, K. F. Microreaction engineering − is small better? *Chem. Eng. Sci.* **2001**, *56*, 293−303.

Table 5. **Summary of responses received for scale-up obstacles**



up. The information sought was to provide guidance on the importance of the obstacles encountered in scale-up. A total of 12 replies were received from 7 sites. The responses for the scale-up obstacles are shown in Table 5 as bar charts reflecting the mean quartile responses. A scale of 1−5 was used where 1 = low and 5 = high. The responses clearly show that difficulties associated with mixing and heat transfer on a large scale are most common to the industry. Particular problems had also been commonly experienced with foam and to a lesser extent solid suspension. The small number of replies may have biased the results, but nevertheless it gives an appreciation of the level of difficulty associated with these potential scale-up obstacles. Many of these obstacles can be broadly assessed if "coarse level information" is available at an early stage. This could help with evaluation of reactor design options. To facilitate this type of information transfer from the physical−organic chemists who participate in chemical reaction system selection to chemical engineers, ultimately responsible for scale-up, a simple questionnaire has been generated and is presented in the Appendix (Supporting Information).

The current industrial practice is a result largely of the recognition that a lot of research at an early stage is wasted due to the high attrition rate of early phase projects. It is therefore imperative that the scale-up approach must make do with the little information that is available from early stage work without incurring added work. This does not imply a change in the work process, as existing experimentation may be better performed by subtle modification to support both the organic chemists' desire for material production and the engineers' desire for data. The difficulty in crossing the skill background exists, as does a historical lack of people with engineering training in the industry, such that those that are employed are often placed in necessary production functions rather than applied research. To some extent the use of robotics and statistical matrix experimental design will assist with the scale-up process by allowing a great breadth of data to be gathered and stored. These data can then be mined to determine fundamental parameters such as activation energies, heat capacities, etc. The requirement is then that early-phase experimental work is conducted in such a fashion to support later-phase development work. This should imply that critical data are able to be extracted from all synthetic work but begs the questions: "what is the critical data?"; "when is the data critical?"; and "to whom is the data critical?"

Conclusions

Both single-phase and multiphase reaction systems can exhibit difficulties in scale-up due to local inhomogeneity. This can normally be tolerated if it occurs in a reagent phase but not if it is in the phase where the main reaction is occurring. The chemist needs therefore to consider how and why reactants come together and react and the full consequences on the reaction rate of the choice of the physical form of reactant, whether it be solid, soluble liquid, immiscible liquid, or gas.

The rate of production in a vessel is often less than the inherent reaction rate due to the need to maintain the reaction mass within some bounds such as limiting temperature, off-gas flow rate, reaction mass volume, etc. Where these limitations have been struck during scale-up, the scientist should review the reasons for these limitations and see if they can be avoided, minimised, or profited from by appropriate engineering design changes. In order then to provide satisfactory design, a detailed knowledge of the difficulty is required. In some cases the literature provides suitable models and correlations to assist in design; for other problems extensive experimentation will be necessary to allow confidence in designing new equipment to handle the difficulty.

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Supporting Information Available

Appendix. This material is available free of charge via the Internet at http://pubs.acs.org.

NOTATIONS

a = specific interfacial area [$\mathrm{m^{-1}}$]
a_p = particle specific surface area [$\mathrm{m^{-1}}$]
B = constant in the Froessling correlation for mass transfer [unitless]
C = impeller bottom clearance [m]
C_i = reagent concentration at the solid−liquid interface [$\mathrm{mol\ L^{-1}}$]
C_∞ = reagent concentration in the bulk liquid phase [$\mathrm{mol\ L^{-1}}$]
c_{A0} = initial concentration of component A [$\mathrm{mol\ L^{-1}}$]
c_p = specific heat capacity, J/kg K
D_L = liquid-phase diffusivity [$\mathrm{m^2\ s^{-1}}$]
d_a = agitator diameter [m]
d_p = particle diameter [m]
d_r = stirred tank diameter [m]
d_t = reactor diameter [m]
d_w = tube wall thickness [m]
d_{32} = sauter area/volume mean diameter
H = Henry's law constant [$\mathrm{Pa\ mol^{-1}\ L}$]
h_r = heat transfer coefficient on the agitated side of a stirred vessel [$\mathrm{W/m^2}$]
h_j = heat transfer coefficient on the jacketed side of a stirred vessel [$\mathrm{W/m^2}$]
g = gravitational acceleration [$\mathrm{m\ s^{-2}}$]
K_L = overall mass transfer coefficient based on the liquid side [$\mathrm{m\ s^{-1}}$]
k = solid−liquid mass-transfer coefficient [$\mathrm{m\ s^{-1}}$]
$\bar{k}$ = average mass transfer coefficient for dissolution [$\mathrm{m\ s^{-1}}$]
k_G = individual gas-phase mass transfer coefficient [$\mathrm{kmol\ m^{-2}\ Pa^{-1}\ s^{-1}}$]
k_L = individual liquid-phase mass transfer coefficient [$\mathrm{m\ s^{-1}}$]
k_r = reaction rate constant [$\mathrm{mol}^{1-n}\ \mathrm{L}^{n-1}\ \mathrm{s^{-1}}$]
M = molecular weight of solute [$\mathrm{g\ mol^{-1}}$]
N = rate of mass transfer per unit volume [$\mathrm{mol\ L^{-1}\ s^{-1}}$]
n = stirrer speed [$\mathrm{r\ s^{-1}}$], order of reaction [unitless]
n_f = stirrer speed for gas flooding [$\mathrm{r\ s^{-1}}$]
n_{JS} = critical stirrer speed for complete off-bottom suspension [$\mathrm{r\ s^{-1}}$]
P = stirrer power requirement [W]
P_G = stirrer power requirement for gassed agitation [W]
Q_G = volumetric gas flow rate [$\mathrm{m^3\ s^{-1}}$]
r_A = rate of reaction of component A [$\mathrm{mol\ L^{-1}\ s^{-1}}$]
S = constant for the Zwietering's complete solid suspension correlation [unitless]
t_d = time required for complete particle dissolution [s]
t_m = characteristic bulk mixing time [s]
U = overall heat transfer coefficient [$\mathrm{W/m^2}$]
u_t = terminal settling velocity for a spherical particle [$\mathrm{m\ s^{-1}}$]
V = volume [$\mathrm{m^3}$]
V_{fd} = volume fraction of the dispersed phase [unitless]
V_L = liquid volume [$\mathrm{m^3}$]
υ_o = liquid volumetric flowrate [$\mathrm{L\ s^{-1}}$]
υ_s = superficial gas velocity [$\mathrm{m\ s^{-1}}$]
X = weight percent loading of solids = 100 × wt of solid/wt of liquid [unitless]
X_A = conversion of stiochiometrically limited reagent A [unitless]

Greek letters

α = recycle of gas in an agitated vessel [unitless]
ΔC_L = mean concentration difference between liquid bulk and gas−liquid interface [mol/L]
$\Delta\rho$ = density difference between solid and suspending fluid or two liquids [$\mathrm{kg\ m^{-3}}$]
ϵ = specific power [$\mathrm{W\ kg^{-1}}$]: $P/V_L\rho$
λ = thermal conductivity [W/m]
μ = viscosity [$\mathrm{kg\ m^{-1}\ s^{-1}}$]
μ_c = viscosity of the continuous fluid phase [$\mathrm{kg\ m^{-1}\ s^{-1}}$]
μ_w = viscosity of the fluid phase at the wall [$\mathrm{kg\ m^{-1}\ s^{-1}}$]
ν = kinematic viscosity [$\mathrm{m^2\ s^{-1}}$], stoichiometric reaction coefficient [unitless]
ρ_c = fluid density of continuous phase [$\mathrm{kg\ m^{-3}}$]
ρ = fluid density [$\mathrm{kg\ m^{-3}}$]
τ = residence (space) time [s]
τ_E = Eddy engulfment time scale [s]
τ_K = Kolmogoroff eddy lifetime [s]
τ_R = reaction time scale [s]

Dimensionless Groups

Fl = gas flow number: $Q_G/n_f d_a^3$
Fo = Fourier number: $\mu t_m/\rho d_t^2$
Fr = Froude number: $nf^2 d_a/g$
Po = impeller power number: $P/\rho n^3 d_a^5$
Pr = Prandl number, $\mu c_p/\lambda$
Re_p = particle Reynolds number: $d_p u_t/\nu$
Re = impeller Reynolds number: $n d_a^2/\nu$
Sc = Schmidt number: ν/D_L
Sh = Sherwood number: $\mathrm{k}d_\mathrm{p}/D_L$

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