Rapid scale-up of pharmaceutical processes- Finding the trees in the forest
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Rapid scale-up of pharmaceutical processes- Finding the trees in the forest

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Abstract

An approach is presented for the management of knowledge gained during the development of pharmaceutical processes. The "Toolbox" approach risk-manages resource commitments during process development by ensuring that knowledge of processing characteristics increases in-line with increasing product maturity. The "Toolboxes" provide an introduction to the basic principles for the novice. This is combined with common laboratory equipment and experimental methodologies to provide a *lingua franca* for engineers working on chemical processes across international borders. Finally, pre-constructed mathematical models have been created to remove the duplication of effort inherent in building and validating scale-up calculations.

Keywords: Batch Process, Pharmaceutical Synthesis, Process Development, Scale-up, Knowledge Management

1. Introduction

The development of chemical processes for the manufacture of pharmaceuticals in early development is fraught with challenge for the practicing chemical engineer, particularly given the attrition rate of projects typical of the industry.

Traditionally, process engineering in the pharmaceutical industry has been focussed on the design and commissioning of process plant for the production of Active Pharmaceutical Ingredients (APIs). Recently there has been a trend to introduce process engineering at a much earlier point in the development life cycle, where process chemists typically dominate the process development (Sherlock & Brewis, 2006). Engineers working in this new arena must often make quick decisions based on little data with the aim of producing robust, scaleable processes.

Processes for the manufacture of API evolve as the candidate molecule progresses through a number of milestones related to proof of safety and efficacy, with the scale of manufacture rising from an initial 1-2kg through to 100-1000kg in the late stages of development. Scale-up is hindered by the small quantities of material available for investigating such problems that may arise. With increasing scale comes an increase in the consequences of a lack of scale-up knowledge, such as incomplete reaction due to inadequate mass-transfer or extended filtration times.

In the forest of potential problems that arise during process development, we must find a way of avoiding the big trees that could cause us serious problems, accepting that the small saplings whilst still part of the forest as a whole, can be brushed aside with minimal resource.

Double et al (2005) have identified the flexibility of the multi-purpose batch reactor in coping with partially developed chemical processes, and it for this reason that Stirred Tank Batch Reactors (STBRs) are the workhorse of the pharmaceutical industry's pilot scale manufacturing capability. This reliance on a common reactor design allows us to thin the forest and focus on the individual trees of consequence by the use of generic approaches since one key variable – equipment type is now fixed.

2. The Process Engineering Toolbox

The aim of process engineering is to apply the use of scientific understanding of scale-up to deliver predictability and manufacturability. For a global company, with development of processes occurring at different geographical locations, it is desirable for a common way of working such that process development can be readily transferred from site to site as and when development capacity requires it.

An internal review revealed that the unit operations most influenced by scale-up were:

1. Filtration
2. Drying
3. Mixing
4. Reaction (specifically hydrogenation)

And additionally that physical property exploitation provided a common foundation for all process development activities.

Crystallisation was also recognized as a unit operation significantly affected by scale-up, but that the scale-up of crystallization can be better served by specialist resource located at each site.

AstraZeneca has developed a series of knowledge bases for the scale-up of frequently used batch processing operations in the areas previously identified. These knowledge bases are designed specifically to ensure that knowledge of processing characteristics increases in-line with the increasing maturity of a product (which therefore has a higher likelihood of reaching the market). Such knowledge bases are known as **"Toolboxes"**.

3. The architecture of a Toolbox

As implemented the toolboxes are web-based, with a common look and feel, so that the user only need be familiar with the architecture of one to be able to use the others with ease.

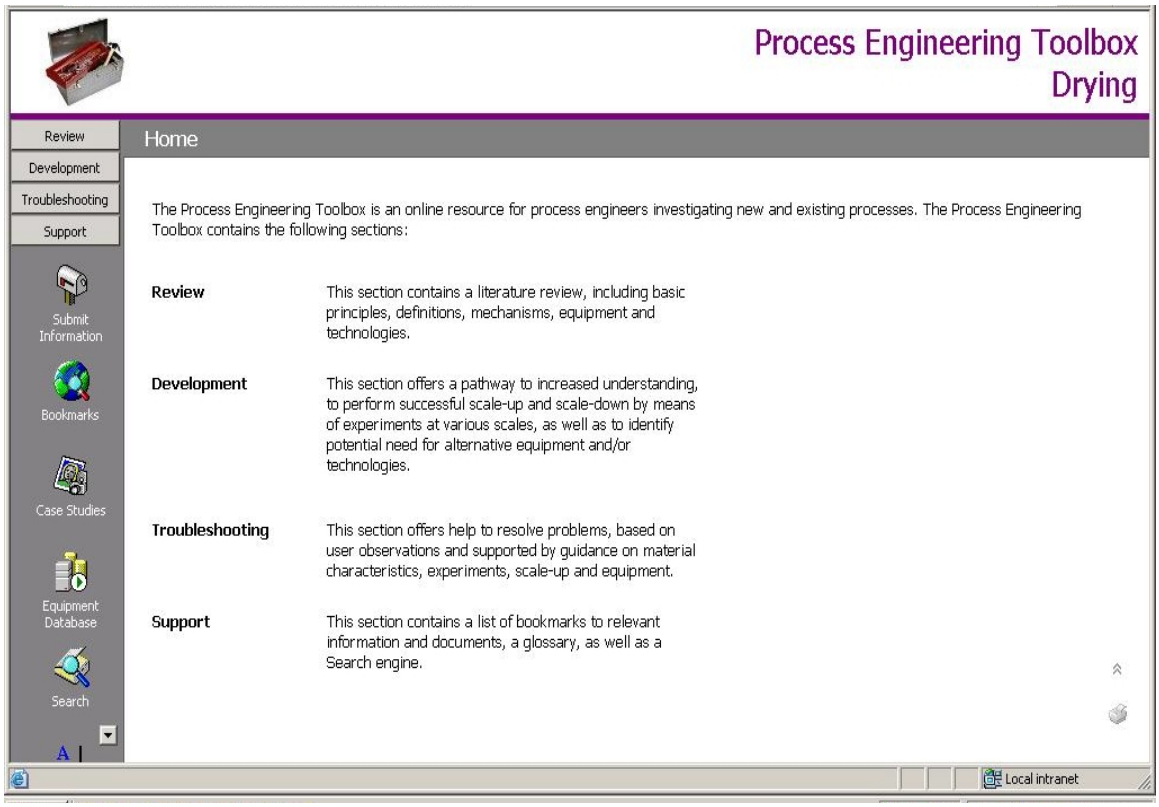

Figure 1 – Toolbox front page

The toolboxes have several distinct sections, the first of which is the review section. This provides the user with a comprehensive guide to the unit operation in question. There is a summary of, and references to the relevant literature, as well as discussing the basic principles of the unit operation, the equipment and technology available in-house and externally for all scales from laboratory screening through to full scale manufacture. This is the first thinning of the forest, since the review section focuses on the relevant processing technologies and techniques that are applied commonly for API manufacture. For example, the filtration toolbox covers classical filtration, but deliberately does not discuss sedimenting filtration as this does not often occur in the isolation of pharmaceutical chemicals.

The development section provides a pathway to understanding the process under consideration. It includes appropriate scale-up / scale-down experimental protocols along with the appropriate time at which to carry them out such that abortive work is not carried out due to the attrition profile of pharmaceutical candidate drugs. This is the second thinning of the forest, and the individual trees are now more clearly seen.

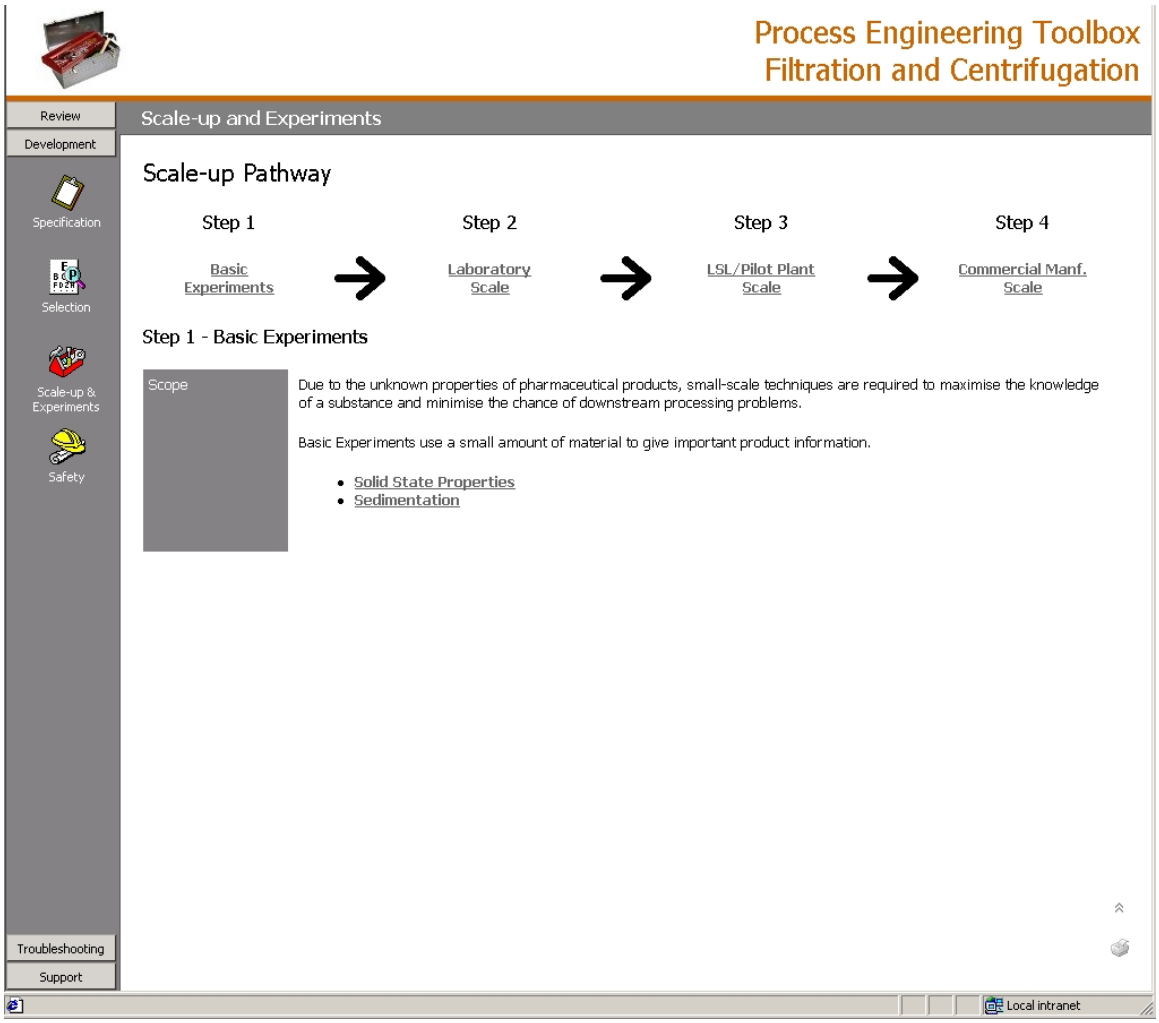

Figure 2 – The scale-up pathway

A key aspect of enabling rapid, robust scale-up calculations is the provision of key equipment parameters for calculation. To ensure that this is efficient, all relevant laboratory, pilot plant and multi-purpose manufacturing scale equipment has its major parameters stored in a database that can be queried from the web page. These can then be used in pre-prepared calculation templates in MathCad or Microsoft Excel format as appropriate. This approach minimizes the amount of effort required to assess scale-up, whilst ensuring that expert knowledge is already built into calculations. The pre-set format also ensures that key assumptions are clearly identified. This section also identifies when traditional processing techniques cannot provide the required capability and highlight the need for the introduction of alternative technologies and equipment.

The troubleshooting section contains practical advice on the diagnosis and remedy for common processing problems that can occur with scale-up, equipment, and experimental procedures.

The final section, support, contains links to all of the electronic information stored in the toolbox, a glossary of common terms and definitions to provide the *lingua franca* for the unit operation, a search engine that allows the toolbox to be searched directly, and most importantly a link to case studies that are used to identify and record unusual or unexpected events. This is the key section in knowledge management, since any user can submit new case studies directly to the toolbox, which is dynamically updated without recourse to republishing the web page.

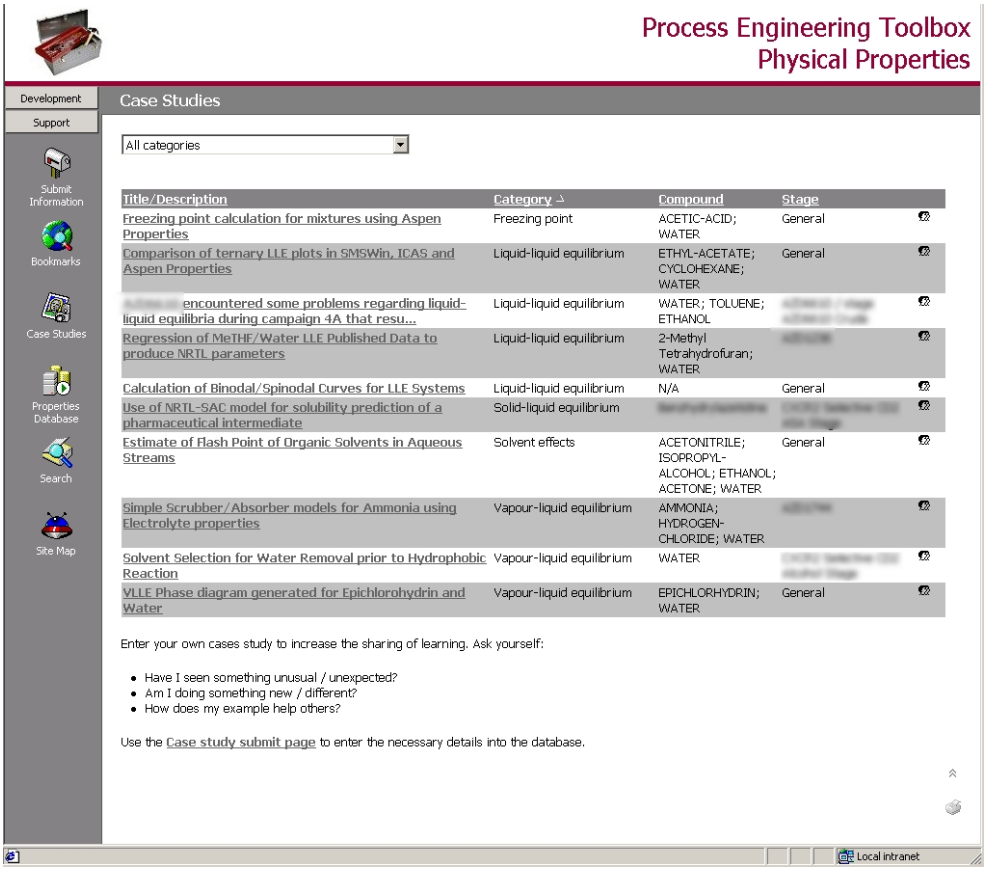

Figure 3 - Case study toolbox page

4. Use of the Toolboxes – scale-up of a hydrogenation

The use of the toolboxes is best illustrated through case studies.
Consider the following:
In the scale-up of a hydrogenation, a process engineer is required to scale-up a nitro reduction reaction from a 1-litre laboratory scale preparation to a 500-litre pilot plant manufacture.

- The reaction in question uses a heterogeneous Pt_2O catalyst and is highly exothermic.
- The catalyst in question has low activity; poor selectivity and cleaning problems are anticipated such that it is desirable to change the catalyst.

- The process engineer has never developed a hydrogenation before.

Step 1 – Get an overview of hydrogenation basics

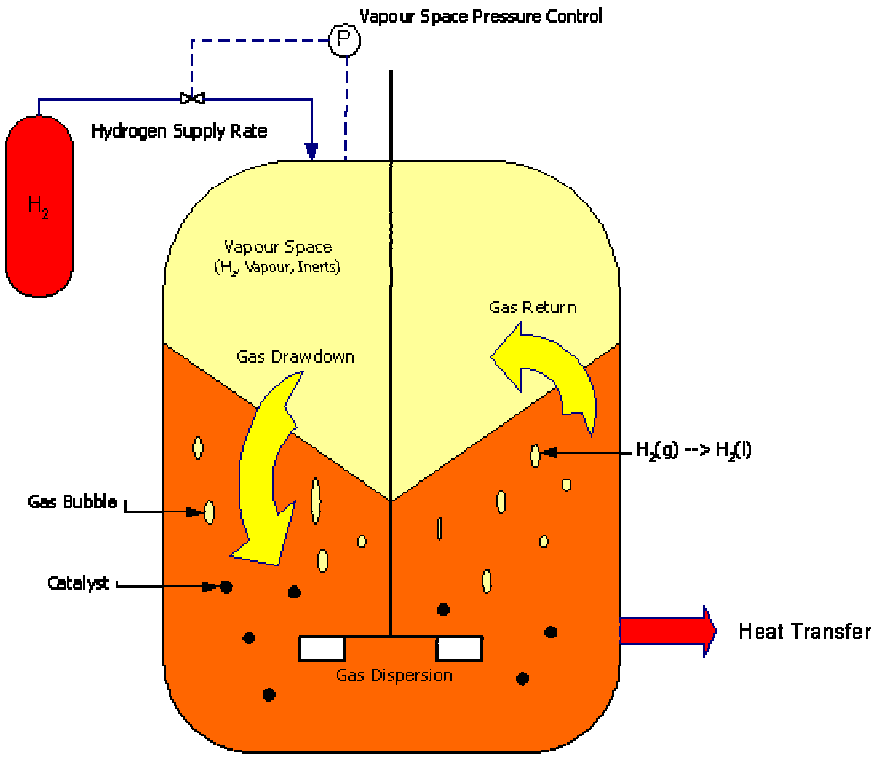

Figure 4 – Hydrogenation schematic overview

The review section of the hydrogenation toolbox gives an introduction to the fundamental processes that influence the progress of a hydrogenation. These are the physical (heat and mass transfer) and chemical rate processes involved and details as to how a typical hydrogenation is run at scale within AstraZeneca are also included.
The effect of scale-up on each of these rate processes is discussed as well as that on the overall hydrogenation reaction.
Once the engineer has an appreciation of the basics, they can progress to step 2.

Step 2 – The Scale-up flowchart

An abbreviated version of the scale-up flowchart is given in Figure 5 , but the aim here is to provide a step-by-step guide to developing and scaling-up a hydrogenation reaction. Steps 3 to 10 are then all contained within figure 5, which, in the live toolbox has embedded hyperlinks to a more detailed explanation of each step.

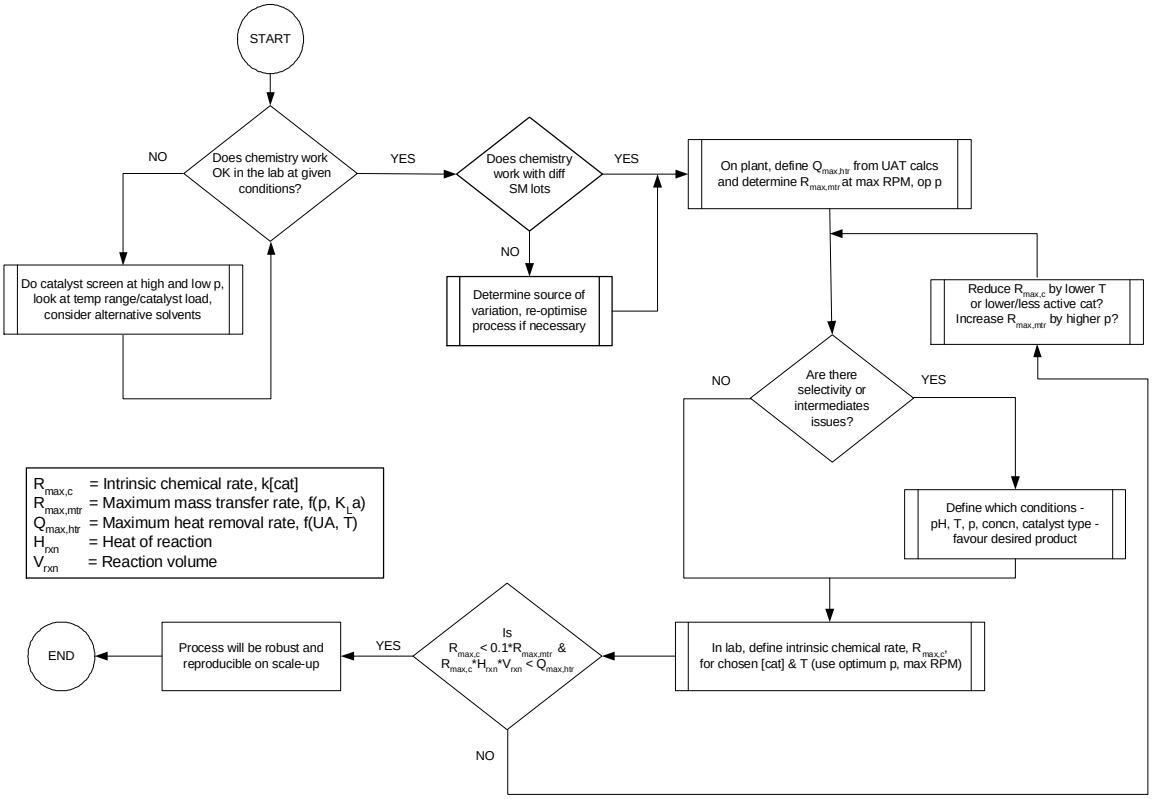

Figure 5 – Abbreviated scale-up flowchart

Step 3- Catalyst, temperature and pressure screening

The toolbox advises a series of screening experiments using one of the Argonaut Endeavour parallel hydrogenators (2-5ml working volume) that are available at each site.

- In this case an alternative Pd/C catalyst and higher temperature gave a 10-fold increase in activity, with a 3-fold reduction in and undesired impurity.

Step 4 – Reaction Robustness

The toolbox then advises a check on reaction robustness, by varying the source of starting material such that any poisoning effects may be seen

- In the case study, no susceptibility to variation in starting material was seen

Step 5 – Determine maximum transfer rates fro plant equipment

Experiments and calculations are provided in the toolbox to characterise the maximum mass transfer rate and heat transfer rates for a plant scale hydrogenator.

In this case k_la is determined by batch absorption and UA is determined by evaluating a step-change in the vessel jacket set point.

Step 6 – Determine the intrinsic reaction rate

Once the optimised reaction conditions have been determined, the intrinsic chemical rate may be found at the intended catalysts loading.

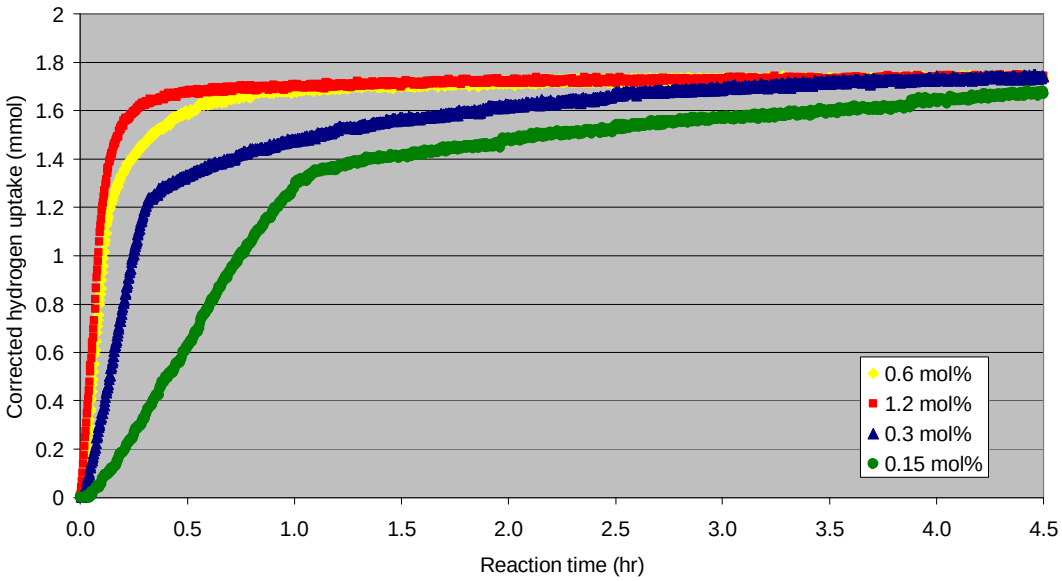

Figure 6 – Hydrogen uptake vs time for varying catalyst loading

Figure 6 shows the results of experimentation using the Endeavour parallel hydrogenator. By taking the derivative of the uptake /time at multiple catalyst loadings, the initial rates can be found. Figure 7 shows a plot of initial rate vs. catalyst loading to determine the linear region where the intrinsic kinetics can be seen without any mass transfer effects.

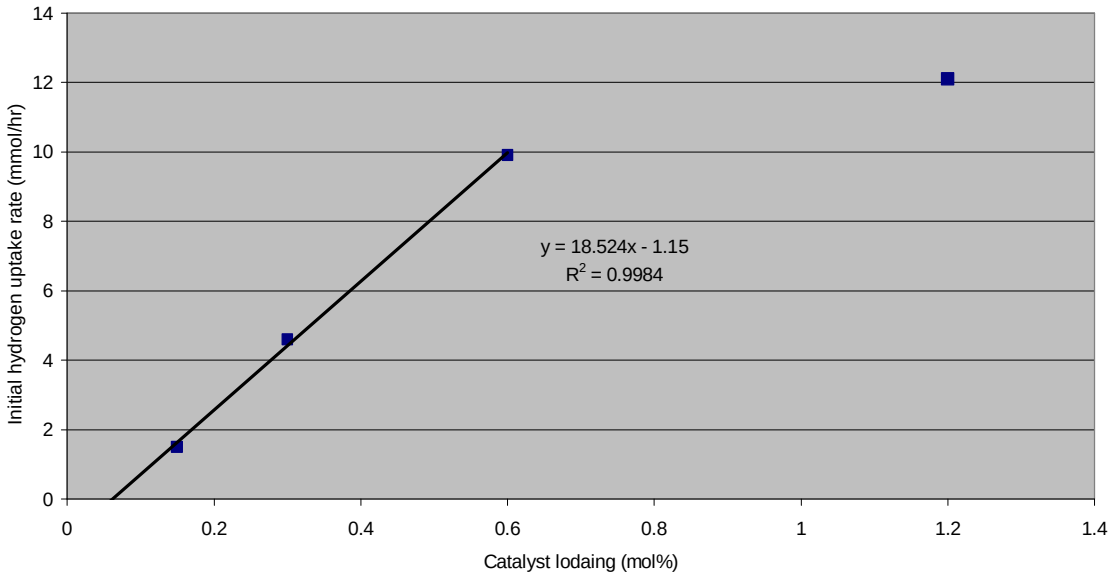

Figure 7 – Initial Rates vs.catalyst loading

Step 7 – Evaluate the maximum heat generation rate

The next key step advised by the toolbox is the maximum heat generation rate, Q_{rxn} from the intrinsic reaction rate and the heat of reaction.

Step 8 – Evaluate whether the exotherm can be controlled

Comparing the maximum heat generation rate with the maximum heat removal rate allows the determination as to whether the exotherm from the reaction can be safely controlled.

- In the case study, heat generation was less than the available heat removal capacity

Step 9 – Evaluate whether the reaction is mass transfer limited at scale

Comparing the intrinsic reaction rate with the mass transfer rate at scale illustrates whether the reaction will be mass transfer limited

- In the case study, the rates are a similar order of magnitude, indicating a potential problem.

Step 10 – Define a strategy to ensure that scale-up will be robust

Several options can be investigated now that we have identified a potential problem – the toolbox provides guidance and suggestions as to how to resolve them:

- Can the mass transfer rate be increased by operation at a higher pressure?
  - Increasing the pressure by 20% still results in a potential problem
- Can reducing the catalyst loading lower the intrinsic rate?
  - As the current loading is only 0.3mol%, there are concerns that poisoning could affect the reaction
- What are the consequences of a mass transfer limited reaction?
  - A high fill volume / low agitation experiment designed to mimic poor mass transfer gave the same selectivity, so a mass transfer limited reaction does not cause a problem

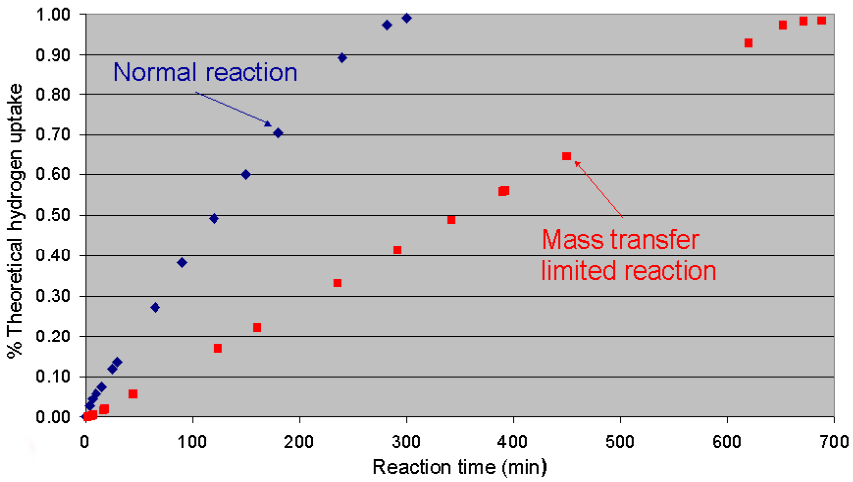

Figure 8 – Reaction profile for normal and mass transfer limited reactions

Figure 8 shows the hydrogen uptake over time for both a "normal" reaction as optimized through the toolbox methodology and one that is mass-transfer limited by design using high volume fill and low agitation rates). The rate for the mass transfer limited reaction is about one third of the normal, chemically limited reaction, but no build up of intermediates was seen during reaction profiling and product purity was equivalent.

Case Study Conclusions

The case study has demonstrated through the use of the toolbox methodology that selection of a new catalyst has improved operability and increased both selectivity and activity. The reaction conditions were optimized in the laboratory to increase selectivity and define the catalyst loading.
The laboratory process has been re-defined so that it will scale-up safely and robustly to pilot plant scale, although the reaction rate may be lower

5. Conclusions

This paper presents an approach to the management of knowledge so that new processes can be rapidly scaled-up with the minimum of risk. This approach has been successful over the last 3 years since launch, with development teams referring to at least one of the toolboxes. This means that the process engineering function within AstraZeneca is now delivering a consistent methodology across projects and international borders. As more projects use the toolboxes, additional case study data is gained and stored within the system so that the learning derived is retained.

The process engineering toolboxes are seen as a useful approach to the de-risking of process scale-up without the expenditure of significant resource.

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References

Double, J.M., Gourlay, B, & Atherton, J.H. (2005) Survey of process intensification equipment requirements, 7th World Congress of Chemical Engineering Proceedings, 0156-003, IchemE, Rugby, UK (ISBN 0 85295 494 8)

Sherlock, J.P., Brewis, L.N. (2006) *AIChE Process Development Symposium,* June 11-14 2006, Palm Springs CA, USA