Chemical Development and Optimisation in Fine Chemical Industry

Dr. S. S. Sakhalkar
RPG Life Sciences Ltd.

★ Chemical development is a difficult area to define covering the whole spectrum of work between research and production but overlapping with both of these disciplines.

★ Chemical development begins at a point at which the active substance has been identified, activity has been demonstrated, and more of the active substance is required. Chemical development is required for longer term work aimed at producing a process, which will work on a plantscale.

★ Where chemical development ends is very difficult to say.The characteristic of any fine chemical industry is continued evaluation of production processes to reduce cost and improvethroughput. Thus, chemical development and chemical manufacture have a great deal of overlap.

★ Even after the production is optimized and the product is already in market there is still need fordevelopment work. A company making a product should always be striving to produce

➧ A cheaper, more efficient process, which may involve a new synthetic route from say newly available raw material or may simply be simpler, more robust manufacturing method.

➧ A less polluting process, so that development chemists need to evaluate ways of eliminating or minimizing toxic reagents or effluent.

➧ A purer product to ensure that waste occurring from batch failing to meet specification is minimized.

★ A major thrust area of chemical development in any company is to use available plant more efficiently -In fact here in lies the skill of the process development chemist. He should be able to design his process to the existing facilities in the company so that unnecessary investment is avoided; right from the beginning of the chemi cal development stage.

Development and Optimisation

Chemical development involves not only synthetic route selection, but also optimisation, scale up and further improvement of the synthetic method until a routine and efficient process, suitable for manufacture by operators, who are skilled but have little chemical knowledge, is obtained. The development chemist's task is to convert a laboratory synthetic route, which uses complex and expensive reagents to a robust manufacturing method which is efficient and uses cheap raw materials and reagents.High yielding chemical reactions producing high quality intermediates and products in tonnage quantities are the development chemist's target. Speedy plant throughput, safety of operations and cost of production are all considerations, which must be borne in mind during the development phase.

Often, time is of the essence -nowadays the development process for new compounds is long so that the development chemist must try not to be the rate determining step in getting a new substance on the market. This may mean compromise -the chemist must be prepared to scale- up his process before it is fully optimised (provided it is safe to do so!) so that batches of new substance for testing programmes are made available on time. However, this can bring benefits; the effect of scale-up on the chemical reaction is demonstrated at an early stage and gives ample opportunity to rethink and to carry out more detailed laboratory development before further scale up may be required.

This is one of the more demanding but also more satisfying areas of chemistry. The extra restraints of tight time scales, increased safety considerations, and rigid analytical specifications place additional demands on the development chemist. The rapid development over the last 20-25 years of analytical methods (particularly HPLC) for quality control of new materials has increased the complexity of the development process. Prior to the routine use of HPLC in quality control, new compound purity was assessed by assay methods such as titrimetric analysis and ultraviolet spectroscopy (which may assay impurities of similar structure to the substance) with impurity profiles being monitored by TLC. Whilst TLC is an excellent method for quick and reproducible qualitative analysis, it has only been useful for quantitative analysis in recent times. The advent of HPLC has provided the analyst with reproducible and quantitative methods of checking assay and impurity profiles so that, with TLC as a back-up, impurity profiles and specifications can be

more strictly controlled. Regulatory authorities are now requiring tighter specifications for new chemical entities,with specifications being controlled by detailed HPLC analysis of impurities and, for example, compounds present in >0.1% in drug substances often need to be isolated and characterised. New peaks at levels above the 0.1 % level are generally considered to be inadmissible. As a result, to ensure a new manufacturing method gives material which passes these tighter specifications, the chemist has to be able to produce high purity compounds routinely in the 99-99.5% range as standard, and this has implications for the control of processes in plant and the instrumentation and methodology used. The advent of HPLC has had its bonuses too. Quality control of intermediates is easier, and it is now possible to detect likely problems, at an earlier stage in the synthesis.

The Development Process - A Multidisciplinary Effort

Process development and scale-up require multidisciplinary co-operation between organic chemists, analytical chemists involved in quality control, and process engineers involved in plant trials, plant modification or new plant construction. Development and scale-up in the pharmaceutical industry requires even further collaboration with pharmacists, pharmacologists, toxicologists, clinicians and marketing specialists to ensure the quality and quantity of drug substances are produced efficiently to an agreed programme over a number of years. Factors, which often cause communication barriers in the development programme, are:

1. The long lead times necessary to make even a few kg of new substance and the difficulty, particularly at an early stage when a synthetic route for scale-up may not be available, of predicting when quantities of material will be available.
2. The difficulties in long term prediction of likely quantities of new substances, so that the chem ist can plan ahead with his supplies campaign.
3. Quality differences between batches within the same specification.

It is therefore important that clear objectives and provision time targets are set well in advance and that project planning involves periodic review of these targets.

In order to meet these targets the development chemist must compromise the need to optimise each of the synthetic steps prior to scale-up and the needs of the project timetable, which may require materials for toxicological or carcinogenicity testing for clinical trials. Inevitably this means the chemist has to proceed with scale-up into the pilot plant with a partially optimised process, i.e. with the best method, which is best to scale-up. Further optimisation can then be carried out later.

The first 10-20 kg of new substance are often the most difficult to obtain. If a new synthetic route is not required, or is required but is not yet available, the method used earlier to make the first few grams must be optimised and scaled-up, even though this is not necessarily the method of choice in the long term. More typically a new synthetic route will be evaluated but a conflict between the time taken to prove the route and the need to scale-up quickly to make the 10-20 kg of new substance will need to be resolved.

In the early stages of development, it may be difficult to guarantee the quality of first batches of final product and often multiple recrystallisation is needed to give material of adequate quality.

Optimisation of Synthetic Routes

Optimisation of a synthetic route used to make a new substance involves not only maximising the yield (and quality) at each synthetic step, but more importantly in producing a product of acceptable quality at the minimum cost, as measured at the manufacturing site. The importance of process costing in optimisation is therefore emphasised, and economic factors may outweigh chemical reasoning. For example a chemical reaction which gives a 90% yield of product in DMF as solvent but involves a tedious aqueous drown out and extraction in the work up may be superseded by a process which uses toluene as solvent, gives only 75% yield but the product crystallises from the reaction, mixture. Solvent recovery and effluent control will also be much simpler in the second process. Thus, simplification of the process is often important.

When material costs in the process are high, the "residence time" of that process in the manufacturing plant may not significantly affect the overall cost of the product, but may impinge on the plant's ability to meet market demand, and to produce a product to tight time schedules. Plant throughput must therefore be a long term

consideration, and is important inall manufacturing processes. When material costs are low, minimisation of plant occupation (i.e. reduction in plant overheads) is probably the most important factor in optimisation. Process costing in the early stages of development can often highlight the areas in the process where attention 'needs to be directed. Often the chemistry is good, leading to high solution yields, but the work up and isolation leads to wastage.

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Before beginning optimisation, an overview of the synthetic route is advisable particularly if rapid scale-up is required and safety considerations may be of vital importance. This overview will enable decisions on where, finite resources available are to be placed.

Some questions, which have to be asked, are

- What needs to be changed to make the process safe to scale-up?
- Are potentially hazardous raw materials, reagents and intermediates involved?
  Can they be substituted? Do the intermediates need to be isolated?
- Is the order of steps most appropriate for the syn thetic route; can some steps be eliminated?
- Can steps be easily combined?
- Are the raw materials available on the scale re quired or do they need synthesising?
- Is the route likely to lead to the presence of highly toxic impurities (or heavy metals) in the final product?
- Are the byproducts likely to lead to effluent problems?

Although all these questions need to be asked, and they may delay scale-up, it is unlikely that they will result in the process being abandoned. Almost any process can be scaled-up in properly engineered equipment if procedures are strictly adhered to, but the cost implications may be, prohibitive. As a result, many processes involve so-called hazardous reagents such as boron tribromide, substituted diazomethanes, thallium reagents, sodium-liquid ammonia reductions, phosgene, alkyl lithiums, hydride reagents and ozonolysis, which, with good engineering can be handled safely on the tonnage scale. Even if expertise is not available in-house, contract companies having particular expertise in a particular area may need to be involved.

In some cases, problems such as likely effluent difficulties may lead to alternative routes being evaluated. For example, in the process development in synthetic routes to ICI's H -antagonist, tiotidine, which was abandoned in 1980 owing to toxicological problems, the initial process involved release of 1kg of methyl mercaptan for every 2kg pure product in the reaction. This was a major factor in the selection of an alternative reagent.

Usually, however, process optimisation concentrates on yield improvements and streamliningthe process.

Yield Improvement

Yield improvement depends on choice of reaction conditions and on accurate (fine) control of parameters, i.e. attention to detail. In order to improve yields it is vital to have an accurate assessment of the yield in each reaction. Therefore a prime requirement is an analytical assay method and a reference standard; the latter may be an arbitrary laboratory sample against which all others are referenced but preferably a highly purified sample of the intermediate or final product. So often, yields quoted on an isolated weight basis can be misleading owing to the presence of inorganics or from the HPLC purity not being measured against a standard, i.e. long running impurities may not have been eluted.

Yield improvement can be carried out either using an investigative approach or empirical methods such as simplex and factorial design based on achieving the maximum yield in the minimum of experiments. The skill in the latter methods lies in the choice of parameters to optimise.

The Investigative Approach

Firstly, for each stage, it is important to find out where the yield was "lost" i.e. to obtain a material balance.

The following questions should be addressed:

1. Has the reaction gone to completion? Is there any starting material left?

If a reaction has not gone to completion (assuming adequate time has been given), it may be that not enough reagent is present or that reagent is being consumed in a side reaction or on further reaction with the product. These factors may be different if the order of addition is changed or if the conditions are changed. Adventitious water either in reagents or solvents can also lead to decomposition of reagent, so it is important that all reagents/solvents are analysed for purity.

2. Was the product formed but further reacted to give a byproduct?

Further reactions can often be detected by examining the effect of extended reaction time on impurity levels. If secondary products are a problem to separate, it may be advantageous to carry out the reaction with a slight deficiency of reagent, particularly if separation of starting material and product is relatively straightforward.

3. What byproducts are formed and how can they be minimised?

Isolation and characterisation of byproducts is one of the most valuable exercises in chemical development. They are best isolated by chromatography of samples, enriched' in byproduct, obtained by recrystallisation of the crude product followed by evaporation of mother liquors. The structure of byproducts can give valuable mechanistic information about the course of the reaction and allow a choice of reaction conditions so that byproduct formation can be, minimised. Occasionally, byproducts are formed by addition of solvent (e.g. exchange of esters with alcoholic solvents) or by impurities in the solvent (for example, dimethylamine in DMF or acetone in isopropanol reacting with carbonyl compounds).

Impurity characterisation is also important in deciding on criteria for intermediate purity. Often, during the early stages of development,' the chemist does not know how pure is intermediates need to be to give final substance of adequate purity. Initially, therefore, a cautious approach is adopted and intermediates are upgraded by recrystallisation at strategic points in the synthetic route. Once the structure of impurities is known, however, it may be realised that they can be left in the intermediate, since they may not react at the next stage.

Characterisation of impurities allows the work up to be designed specifically to remove that impurity. On occasions careful pH control of the aqueous phase during an extraction (based on the pKa of the impurity) will allow a separation method to be devised. Additional choice of recrystallisation solvent is aided by knowledge of the solubility properties and the structure of impurities.

4. Did the reaction go to completion but the product was lost during work-up?

Product isolation is one of the most vital - and one of the most underated -areas in development. Work-up of a process needs careful design and should consider safety factors and ease of scale-up. Often, unstable products can be hydrolysed during aqueous work-up, the problem being accentuated during scale-up. It is important to establish, therefore, a material balance to determine how development of the process should be carried out. The solution to a low yield problem may be as simple as a change in recrystallisation solvent or a change in extraction conditions (e.g. change of pH, salting out. Relative ratios of solvent and aqueous layers, reducing emulsions). If the work-up is likely to be a problem, then serious consideration should be given to combining stages.

Streamlining the Process

Further development of a synthetic route, even when the yields in each step are high, can reduce the cost of a new product substantially and impact greatly on the introduction of the process into routine production. Many of the factors below may help to improve the yield, but not all will do so; they may, however, improve throughput in the plant by improving "volume efficiency" and by process simplification. Factors which may need to be varied (possibly using a statistical approach) are discussed

below, and a rational approach to variation of conditions is an essential part of optimisation.

1. Change of Reagent or Catalyst : At the early stages of development, the chemist may wish to change the reagent to improve yield or increase selectivity; towards the end of the development, cost reduction or effluent control may be the prime motive. An example of the importance in a commercial process was in the scale-up of the manufacture of the Merck drug, cefoxitin, where the change from a complex catalyst (N-silyl-trifluoro-acetamide) to a cheaper and simpler material (powdered molecular sieves) allowed not only the required acid protecting groups to be removed, but also meant that a simpler amine protecting group could be used in the sequence. However, further scale-up indicated that batch to batch differences in the molecular sieves exert an unacceptable variation in the process and the ultimate reagent chosen was the soluble catalyst trimethyl-silyl methyl carbamate.

2. Minor Changes of Intermediate : Although the synthetic route may remain substantially the same, it is possible to affect significant improvements by a minor change in the intermediate, i.e. by varying one of the following:

a) Change in protecting groups
b) Change in the ester to increase/decrease rate of reaction, improve selectivity
c) Change in salt form of the intermediate, possibly to improve ease of isolation
d) Change in leaving group to increase rate of reaction or to circumvent a possible effluent problem

3. Solvents : These are dealt with in a separate section.

4. Stoichiometry : Changing the relative ratios of reagent (and occasionally so-called catalysts) to raw material usually has a profound effect on the course of reaction and may allow a reaction to be driven to completion. Excess of reagents, however, may hinder work-up (e.g. excess aluminum chloride in Friedel-Craft reactions usually drives the reaction to completion by complexing with the product, but work-up is often difficult) and a balance has to be found. Sometimes excess of reagent may be detrimental, for example where it reacts with the required product (e.g. in oxidisation of sulphides to sulphoxides) and this over reaction may need to be carefully controlled. An essential part of this control would therefore be accurate assay methods for both reacting components.

5. Rate and order of addition of reagent or catalyst : The rate and order of addition of reagents is often changed by development chemists to assist in the ease of handling on the plant,' or to aid the control of exotherms, but may have a fundamental effect on the course of some reactions (e.g. Friedel-Crafts reactions). It is essential that the effect of these factors on yield and byproduct formation is examined prior to scale-up.

6. Temperature : Increasing temperature obviously will increase the rate of a reaction but often selectivity is reduced. Conversely, reactions are usually carried out at low temperature to improve selectivity. Very low temperatures (e.g.-78°C) are rarely used in scale-up, and many reactions carried out in the literature at -78°C (e.g. butyl lithium reactions) can be carried out with similar results at -30°C, this being within the capability of normal batch processing equipment.

Accurate and reproducible control of temperature, particularly during exothermic reactions is a typical part of scale-up and the effect of temperature on reactions should be examined for hazard evaluation even if no yield or throughput improvement is envisaged -occasionally surprisingly results are found. For example, the well known formulation of ketones and esters with sodium hydride and ethyl formate proceeds rapidly at 0-10°C and gives high yields of formylcarbonyl compounds. At 50°C, however, it was found that no product was obtained, because ethyl formate is decomposed at this temperature by the hydride to give sodium ethoxide and carbon monoxide. This study does suggest, however, that the reverse process may be valuable, and that carbon I monoxide in the presence of a strong base may be useful formulating conditions.

7. Pressure : Pressure is rarely considered by chemists as a variable except when reactions such as catalytic hydrogenation are being carried out. Only very high pressures (10-20 kbars) will affect solution phase reactions, but recent interest in the subject and the availability of cheaper specialised equipment may mean that in the future, the development chemist may need to use pressure besides temperature as a means of improving selectivity (for example in cycloaddition reactions).

8. Time : In plant terms, time costs money, so that any factor which will decrease the plant occupation

time will result in cost reduction. Inevitably this means studying temperature and concentration variability. In this context it is important to have an accurate method (usually tlc or HPLC) for checking completion of reaction thus allowing work-up to take place as soon as possible. Simplification of work-up is also usually the best method of minimising plant occupation.

9. Concentration : Study of the effect of concentration on yield and quality of product is vital to improve volume efficiency and minimise costs. The volume efficiency of a process is defined as the amount of product, which can be produced in unit volume of reactor in unit time. It is thus a measure of plant throughput and is important at all stages of chemical development. During early development when the process is first scaled-up and time is short for production of early supplied for vital tests, a doubling of volume efficiency may allow tight time schedules to be met. Obviously the main concern is to reduce solvent to reactant ratios, and to reduce work-up volumes, to improve process efficiency. It should also be remembered, however, that increasing the concentration should have the benefit of increased rate of reaction, together with the disadvantage of increased thermal hazard; the lower the solvent volume, the greater the heat evolution per unit volume and the greater the cooling required! Once again a balance has to be found!

Sometimes short cuts taken to improve volume efficiency can have additional benefits. For example, in phase transfer reactions it is often possible to eliminate the use of water and to get even better results. The condensation of aromatic aldehydes with active methylene groups will often proceed with solid sodium hydroxide or carbonate and a phase transfer catalyst in the absence of water.

The above discussion has centred on changing process variables to improve usual yield and often product quality. One factor not discussed above is the effect of raw material (or intermediate) purity on yield, since small amounts of impurities can often have a significant effect on reactions. It goes without saying that a programme of optimisation should, as far as possible, use raw materials of comparable quality (preferably taken from one large batch) but periodic checks over a number of months for changes in quality of raw materials (Has the manufacturer changed or has the specification changed?) or changes in home produced intermediates (does the intermediate deteriorate with time during storage?) are an essential part of any development programme. The importance of analytical methods for quality control of reagents, solvents and intermediates is once again stressed. Use-tests to check the quality of new batches of essential raw materials or intermediates are therefore important, particularly when the supplier will be constantly improving his, process but his quality may vary; occasionally higher quality raw materials give worse results -the trace of acid impurity, for example, can be vital!

Of similar importance is that reactants, catalysts and solvents used in process optimisation are of similar grade and quality to those to be used in the plant, so that a direct correlation can be made. Of course, it is perfectly acceptable for optimisation to take place initially with laboratory quality reagents provided that the reagents to be used on plant are adequately use- tested beforehand.

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Dr.S.S. Sakhalkar has done Ph.D.(Tech) in Pharmceutical Chemistry from the UDCT in 1990. He started his career in NOCIL from 1991 onwards as R&D officer. His basic research area in SHELL NOCIL research programme was on Agrochemical NCE's.

Currently he is working in RPGLS [Formrly Searle(India)] as R&D Sr.Manager from 1996 onwards.