PART II

ACTIVE PHARMACEUTICAL INGREDIENT (API)

6

THE ROLE OF CHEMICAL ENGINEERING IN PHARMACEUTICAL API PROCESS R&D

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6.1 INTRODUCTION

The evolution of R&D and synthetic chemical processing in the pharmaceutical industry in the past century is remarkable in the accomplishments of bringing many important therapeutic products to the world markets.

These successes are illustrated by the proven ability of chemists and chemical engineers to overcome the many process problems that can be encountered in development and scale-up that are critical in bringing valuable therapeutic products to market. Failure to do so could have resulted in some of these products remaining as laboratory curiosities.

One of the outstanding examples of this type of success is illustrated by the penicillin process, in which penicillin could have remained a laboratory curiosity if not for a breakthrough using chemical engineering principles as applied to fermentation processing—further discussed below.

Cost to patients is, of course, a major source of concern for the industry. On the R&D side, minimizations of operating and capital costs are always key objectives in developmental programs. These efforts can at times be frustrated by the rather small impact some improvements can have in reducing costs. In other cases, a therapeutically important product can only be brought to market at a reasonable cost because of the chemical and engineering input in R&D. It is always interesting to speculate how critics decide something is far too expensive without knowing anything about the costs associated with discovering, developing, and making the product.

6.2 CHEMISTS AND CHEMICAL ENGINEERS

A fascinating aspect of the history of R&D and manufacturing is the relationship between chemists and chemical engineers and how this relationship has evolved over the years.

The accomplishments of chemists in the creation and development of complex syntheses provide the foundation of R&D in the Pharmaceutical Industry. It has always been a source of amazement to see how the synthesis of a complex molecule can be achieved from seemingly unrelated parts.

Chemists were unquestionably in charge of R&D through the 1950s and their role in process R&D was then viewed as dominant over chemical engineers. This latter point is well illustrated by noting that the then President of the Research Division, Merck & Co., Inc., Max Tishler, later to become president of the American Chemical Society, personally led the manufacturing plant start-up teams for new processes.

The question may be asked regarding what role chemical engineers have in making these complex syntheses commercially viable. Chemical engineers have played key roles in many processes and the remainder of this chapter will be focused on some aspects of the relationship. Some generalities

R&D has been dominated by chemists.
The role of chemical engineers is less defined.
The role has changed over the years
The role varies considerably between companies.

*Retired

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The challenge to the chemical engineer is to recognize the following:

(1) when a process can just be made larger and therefore be readily scaled to manufacturing or
(2) when some changes requiring specialized equipment and/or process operations are needed for successful scale-up and/or economical operation.

The key to effective engineering input is the organization in R&D that allows for both early involvements in process design and process development. Also, continuing responsibility for plant design as well as the integration of laboratory and pilot plant programs with chemists—all leading to a manufacturing process and plant start-up. Management of these key functions must establish clear lines of responsibility that promote interdisciplinary cooperation. These roles are not difficult to state but can be difficult to accomplish. However, the benefits of this integrated effort can be realization of superior process design and operation.

6.3 PENICILLIN: A CHEMICAL ENGINEERING ACHIEVEMENT

The development of deep tank fermentation technology is cited as an achievement by chemical engineers, which has had a profound impact on both process technology and medicine. In the 1930s, after the discovery of penicillin, the only method to make the antibiotic was in a surface mold that was capable of making only gram quantities.

Surface culture was replaced by deep tank fermentation in the mid-1940s by collaboration between Abbott, Lederle, Squibb, Pfizer, and Merck with consultant Richard Wilhelm, Department Chair of Chemical Engineering at Princeton University. Implementation of this technology was achieved by application of chemical engineering principles developed in the 1930s and 1940s. Without this innovation, penicillin would have remained a laboratory curiosity for an unknown length of time. All subsequent antibiotic fermentation processes have utilized this technology.

In addition, the processing of large volumes of fermentation broth was achieved by continuous filtration and extraction. The following citation captures the extent of these accomplishments.

The American Chemical Society, in collaboration with the Royal Society of Chemistry, designated the development of penicillin as an International Historic Chemical Landmark on November 19, 1999. The text of the plaque commemorating the event reads

> In 1928, at St. Mary's Hospital, London, Alexander Fleming discovered penicillin. This discovery led to the introduction of antibiotics that greatly reduced the number of deaths from infection. Howard W. Florey, at the University of Oxford working with Ernst B. Chain, Norman G. Heatley and Edward P. Abraham, successfully took penicillin from the laboratory to the clinic as a medical treatment in 1941. The large-scale development of penicillin was undertaken in the United States of America during the 1939–1945 World War, led by scientists and engineers at the Northern Regional Research Laboratory of the US Department of Agriculture, Abbott Laboratories, Lederle Laboratories, Merck & Co., Inc., Chas. Pfizer & Co. Inc., and E.R. Squibb & Sons. The discovery and development of penicillin was a milestone in twentieth century pharmaceutical chemistry.
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> *Source:* American Chemical Society [1].

The difficulties are summarized in the following quotation:

> Pfizer's John L. Smith captured the complexity and uncertainty facing these companies during the scale-up process: "The mold is as temperamental as an opera singer, the yields are low, the isolation is difficult, the extraction is murder, the purification invites disaster, and the assay is unsatisfactory." American Chemical Society [1].

6.4 BATCH AND CONTINUOUS PROCESSING

It is believed that some of the accomplishments in penicillin isolation were made possible in part because, in the 1940s, academic training in chemical engineering was focused on continuous processing with models from the petroleum industry. Thus, chemical engineers were ready to develop continuous processes since their training would lead them to think—continuous—first.

Batch and semi-batch operation will continue to predominate and are the methods of choice in many processes for readily documented reasons. Efficiency of these operations has been greatly enhanced in recent years by online computer control and analytical instrumentation. Start-up, operation, and shutdown of continuous operations have also been greatly facilitated by computer control. In addition, the small size of most in-line mixing devices can minimize or eliminate off-specification product from unsteady-state operation.

The development and manufacturing utilization of continuous processing in pharmaceutical manufacturing has been successfully accomplished in a variety of process applications. These process options are discussed by Paul and Rosas [9] along with the chemical engineer's role in the development and manufacturing implementation of safe and efficient processes with minimum capital and operating costs. The utilization of continuous operations is included in this developmental strategy, when appropriate to solve scale-up issues that may be encountered in some systems, including reactor selection and design, separation trains, and crystallization operations. In some of these systems, the

inherent limitations of batch operation in mass transfer, mixing, and throughput require continuous operation for successful scale-up of selected steps.

Examples of these options are not limited to throughput efficiencies but, in some cases, include operations that cannot be successfully run batch wise. Examples include (1) fast, complex reactions that require more effective mixing and/or mass transfer than can be achieved in stirred vessels, (2) thermally hazardous reactions in which reaction volume must be minimized, and (3) some crystallizations including the direct resolution of optical isomers or control of particle size within tight limits .

Utilization of these types of process improvements has resulted in manufacturing efficiencies in many processes, as well as in evolution of strategies to integrate the R&D efforts of process chemists and chemical engineers starting early in the development cycle.

6.4.1 Literature

The design and utilization of continuous systems in the pharmaceutical industry has received little attention in the literature as opposed to the chemical industry in general. Since most of the applications are for fast reactions, large scale-up factors are not often encountered. The combination of high heats of reaction, high reactant concentrations, fast reaction rates, and simultaneous or consecutive reactions to undesired products presents an extreme challenge to chemists and development and design engineers. Heat transfer and micro-mixing requirements must be satisfied simultaneously.

The subject of mixing and fast chemical reactions has been extensively covered in the seminal work by Baldyga and Bourne [2], including the development of the test reactions that can be used in evaluation of various types of reactor systems for fast reactions. Mixing issues are also treated in the *Handbook of Industrial Mixing* [8], including several examples.

There are several issues that can lead to the decision to develop a semi-continuous or continuous process versus a batch or semi-batch operation. Each process requirement must be evaluated on the basis of manufacturing scale feasibility.

The most important reactor issue is achieving equal selectivity and by-product distribution on scale-up. For fast reactions, this may require in-line reactor configurations including tubular devices such as static mixers to achieve the necessary mixing intensity to minimize over-reaction in competitive–consecutive and parallel reactions.

Common reactor configurations such as continuous stirred tank reactors (CSTRs), packed beds, fluid beds, and trickle beds that are used in the chemical industry for high throughput find limited utility in the pharmaceutical industry because of reduced throughput requirements. In addition, this type of contacting can be achieved in standard batch or semi-batch reactors, including multiphase reactions, when mixing intensity is not an issue for selectivity on scale-up.

Factors that require evaluation include

highly exothermic reactions,
mass transfer limiting reactions,
thermal hazard reactions,
crystallization at nonequilibrium conditions and with narrow size distribution requirements, and
high throughput requirements in reactions and separations.

The necessity to utilize a continuous reactor to achieve successful scale-up can, in some cases, be determined by analysis of data for a laboratory semi-batch reaction. For a classical consecutive–competitive reaction, the sensitivity to mixing can be evaluated by running the reaction under identical conditions of addition time, temperature, and feed point, but with increased mixing intensity. If the selectivity increases with increased mixing speed, thereby generating smaller amounts of by-products, the reaction is fast enough to be mixing sensitive. If increasing mixing speed does not result in achieving a plateau in selectivity, the reaction may not be scalable in a semi-batch configuration [8].

6.5 EXAMPLES

The following two examples, chosen as illustrations, are focused on R&D issues that required something more than direct scale-up either because

(1) the original laboratory process could not be successfully scaled up and achieve the desired yield or product quality and
(2) the process cannot be run successfully in a batch mode even in the laboratory.

Example 6.1 Alkylation Reaction with Continuous Liquid–Liquid Extraction and Crystallization

This example illustrates a combination of semi-batch and continuous operations in one step of a multistep synthesis (see Figure 6.1). The sequence is as follows

semi-batch alkylation reaction,
continuous multistage extraction (Karr extractor), and
semi-continuous crystallization.

6.5.1 Reaction

The semi-batch reaction is a competitive–consecutive sequence, which is as follows

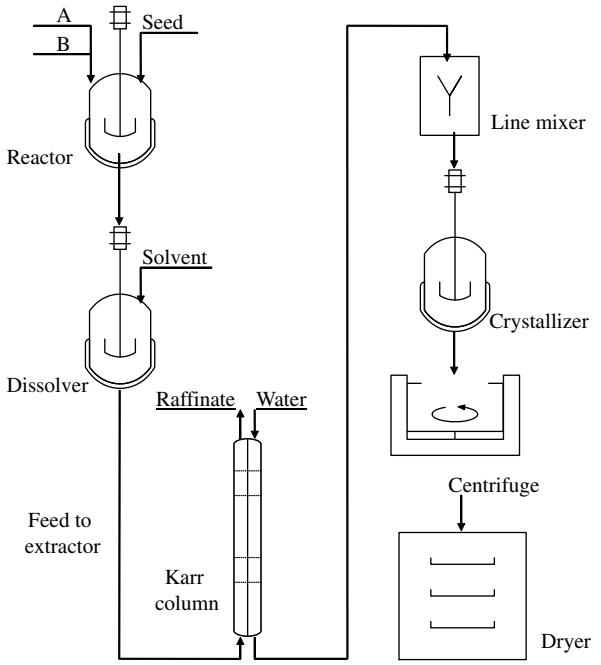

FIGURE 6.1 Flow sheet for alkylation step showing the configuration of reactor, extractor, crystallizer, and isolation.

$$\begin{aligned} A + B &\rightarrow R \\ R + B &\rightarrow S \end{aligned} \tag{6.1}$$

where R is the product and S is the bis over-reaction product. When run as a homogeneous reaction system, the bis formation was excessive. A change to increase the concentration of the reaction mixture was possible to achieve increasing supersaturation of R as the reaction preceded. The addition of R seed at the start of the reaction was implemented to guarantee crystallization of R during the semi-batch addition of B. By separating the R as crystals in a second phase, the bis formation was minimized thereby raising the selectivity of R by $>15\%$. Methods of increasing selectivity in heterogeneous systems are described by Sharma [10].

6.5.2 Extraction

On completion of the reaction, the R crystals are dissolved to prepare for purification by continuous solvent extraction using a multistage countercurrent Karr extraction column, which removes the aqueous-soluble components of the reaction mixture as illustrated in Figure 6.1.

6.5.3 Crystallization

The organic phase containing R and S is fed directly from the extractor to a crystallizer using a line mixer to induce nucleation of R in the feed stream. In this operation, the crystallizing product accumulates in the crystallizer. The required crystallization conditions, temperature, and mixing intensity for controlled nucleation and growth, are maintained in the line mixer between the extractor and the crystallizer. The slurry in the crystallizer is recycled around the crystallizer and through the line mixer throughout the operation.

The operation continues until the solution from the extractor feed tank is consumed and the product has accumulated in the crystallizer. The slurry is then cooled and centrifuged.

Example 6.2 Continuous Operation Required for Process Viability

The following example illustrates a case in which continuous processing is used because batch or semi-batch operation cannot produce the desired separations for the resolution of optical isomers.

This application operates at nonequilibrium conditions, therefore, continuous operation in separate R and S isomer crystallizers is the only feasible method to maintain optical purity in the crystallizers. Batch methods have been described in the literature [7] for laboratory operation but cannot be scaled-up because of the requirement to operate in the kinetic regime to prevent nucleation of the undesired isomer. The method applies only to racemic conglomerates and not to racemic compounds since the separation requires crystallization of each isomer separately, a condition that can only be met with racemic conglomerates.

The system has been described in patents [3–6, 11]. The system is shown in Figure 6.2. The fluidized bed provides the necessary solid–liquid separation between crystal beds as well as a controlled environment for crystal growth with minimum nucleation.

The key conditions for successful operation are (1) close control of supersaturation to prevent nucleation in the respective seed beds and (2) growth of seed crystals that are compatible with fluid bed operation . In addition, since the system is essentially an all-growth operation, the population balance must be maintained by some form of crystal fracture. This fracture is achieved by sonication as described in the Midler patents.

The fluidized bed technology can also be utilized in general for continuous crystallization and is particularly useful for the growth of large crystals for ease in downstream processing as well as for high throughput.

In both of these examples, the role of chemical engineers was critical in realizing the benefits of implementing changes in the original processes. For Example 6.1 (alkylation), the chemistry was established by the process chemists who then followed all aspects of the subsequent development in the

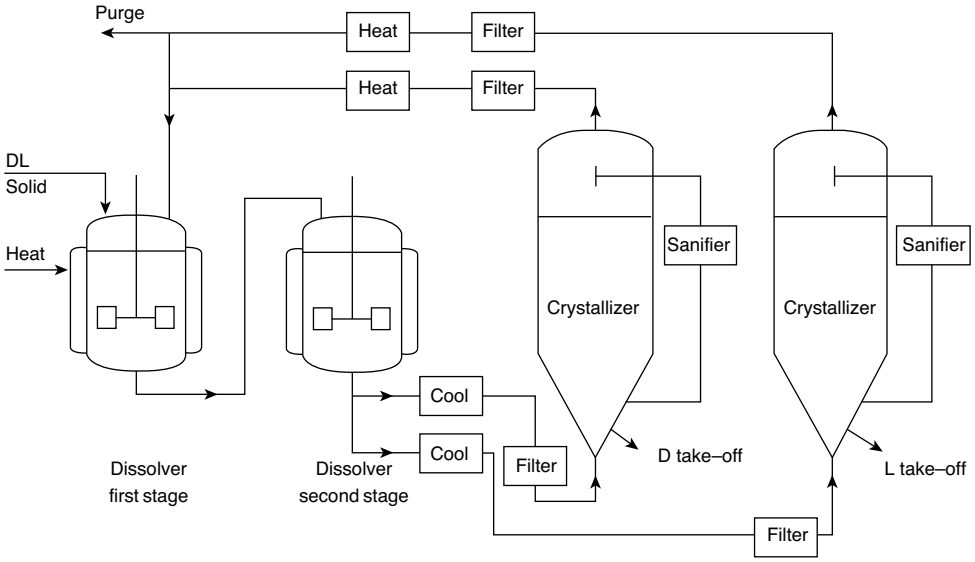

FIGURE 6.2 Flow sheet for resolution of optical isomers by direct crystallization (Source: Ref. 11, Fig. 7-27, p. 163. Reprinted with permission of Wiley).

engineering laboratory and pilot plant as well as participating in the manufacturing plant start-up. Engineering input came in three aspects of this step (1 of 17 steps for this synthesis) (1) selectivity improvement by crystallization to reduce bis formation, (2) process design to introduce continuous extraction and crystallization, and (3) crystallization equipment design to achieve crystal growth required for feasible filtration times on scale-up .

(1) Selectivity increase resulted in improvement of $>15\%$ with the resulting reduction in process cost in this late and critical step.
(2) Continuous operation was critical because of the high production volumes required where multistage batch extraction would be unfeasible.
(3) Crystallization by continuous in-line mixing and maintenance of a large seed bed was critical to both the high production volumes and to overcome nucleation of small poorly filtering crystals and achieve crystal growth.

For Example 6.2, the original processes for which this direct resolution technology was developed, accomplished the resolution through traditional diastereoisomer methods. These methods were successful but added costs through the use of resolving agents and their recovery as well as through multicrystallization and filtration steps.

Engineering input started in the laboratory, in first establishing feasibility for direct resolution—not a feasible option when the isomers form racemic compounds (solid solutions).

This development required the solution of several key issues including (1) solid–liquid separation after partial crystallization of each isomer, ultimately accomplished with fluidized bed technology, (2) development of a solvent system compatible with the solubility of the isomers, (3) establishment of supersaturation limits for operation with minimal nucleation (essentially all-growth), (4) a suitable method of crystal fracture to limit growth in the continuous operation, and (5) development of a control system to maintain the narrow limits of supersaturation and solid–liquid balance in the fluidized beds for continuous operation . The flow sheet is shown in Figure 6.2.

These engineering challenges were met in the evolution of robust processes that have been in large-scale operation for many years.

6.6 OTHER CHEMICAL ENGINEERING ACTIVITIES

The activities of chemical engineers in Pharma extend too many aspects of processing other than to reactions and separations as illustrated above. The range and importance of these activities is well demonstrated in the many topics addressed in this book.

REFERENCES

1. American Chemical Society. *Historic Chemical Landmark*, 2004.
2. Baldyga J, Bourne JR. *Turbulent Mixing and Chemical Reactions*. Wiley, Chichester, 1999.

3. *Chemical Engineering* magazine staff, Kirkpatrick Chemical Engineering Achievement Awards. *Chem. Eng.* 1965; 72 (23): 247.
4. Midler M. Production of crystals in a fluidized bed with ultrasonic vibrations. *U.S. Patent* 3,510,266, 1970.
5. Midler M. Process for the production of crystals in fluidized bed crystallizers. *U.S. Patent* 3,892,539, 1975.
6. Midler M. Crystallization system and method using crystal fracture external to a crystallizer column. *U.S. Patent* 3,996,018, 1976.
7. Mullin JW. *Crystallization*, 4th ed., Butterworth-Heinemann, Oxford, 2001.
8. Paul EL, Atiemo-Obeng V, Kresta SM, editors, *Handbook of Industrial Mixing: Science and Practice*, Wiley, New York, 2004.
9. Paul EL, Rosas CB. Challenges for chemical engineers in the pharmaceutical industry. *Chem. Eng. Progress* 1990; 86 (12): 17–25.
10. Sharma MM. Multiphase reactions in the manufacture of fine chemicals. *Chem. Eng. Sci.* 1988; 43 (8): 1749–1758.
11. Tung HH, Paul EL, Midler M, McCauley JA, *Crystallization of Organic Compounds: An Industrial Perspective*, Wiley, New York, 2009.