23

PROCESS DEVELOPMENT AND CASE STUDIES OF CONTINUOUS REACTOR SYSTEMS FOR PRODUCTION OF API AND PHARMACEUTICAL INTERMEDIATES

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23.1 INTRODUCTION

Batch processing in stirred tank reactors is the default mode of operation for production of process intermediates and active pharmaceutical ingredients in the pharmaceutical industry. This is true for both homogeneous and heterogeneous reactions, as well as the subsequent workup unit operations and final crystallization. While commonplace in the commodity chemical industry, continuous processes are somewhat rare in the pharmaceutical industry. However, the potential advantages of organic synthesis reactions operated via a continuous mode include enhanced safety, improved quality, reduced energy costs, and greater cycle efficiencies [1]. These benefits are largely the result of smaller active reaction volumes and superior mass and heat transfer. Recently in the pharmaceutical industry, there has been renewed emphasis on holistic continuous processing where not only the reaction, but downstream extractions, solvent exchanges, and crystallizations are performed continuously as well [2]. However, most examples of continuous processing in the pharmaceutical industry are reaction only at this point, and this chapter will primarily focus on implementation of continuous reactions.

Part of the appeal of stirred tank batch reactors is their general versatility and the fact that a single piece of capital equipment can serve as a reactor, an extractor, a still, or a crystallizer depending on the needs of the process. This versatility enables a wide array of unit operation combinations and therefore, a single plant with multiple stirred tank reactors can manufacture a large number of products, with different processes. Additionally, batch processing on scale is similar to how a process chemist typically works in the laboratory. For example, charge ingredients, heat to reaction conditions, react for a specified time and sample for reaction completion. This systematic approach affords a simple and reproducible methodology for processing. However, laboratory and manufacturing scale batch reactors typically have vastly different heat and mass transfer characteristics. For chemistries in which heat or mass transfer controls selectivity, a direct scale-up of a laboratory batch process may be problematic in manufacturing. Similarly, limitations in heat transfer in stirred tank reactors may render some energetic laboratory processes unsafe at manufacturing scale. Finally, the versatility provided by general purpose stirred tanks comes at an efficiency cost when compared to continuous equipment designed for a specific unit operation. In each of these instances, continuous processing can offer advantages over traditional batch processing.

This chapter discusses opportunities for continuous processing of pharmaceutical intermediates and API, review some considerations for developing and implementing continuous processes, present two brief case studies from the authors' experience, and consider some of the barriers to widespread use of continuous processes. Since the engineering design equations for continuous reactors are covered extensively in undergraduate Chemical Engineering curricula, that level of detail is not presented here.

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23.2 BENEFITS OF CONTINUOUS PROCESSING

23.2.1 Safety

Process safety is probably the greatest driver for development of continuous processes within the pharmaceutical industry. The two attributes of continuous processes that facilitate improved safety are a reduced inventory of reactive species and improved heat transfer. For a given throughput, continuous reactors are relatively small when compared to batch reactors. Additionally, continuous reactors are often operated at higher temperatures than batch reactors, resulting in higher rates of conversion. Both of these factors reduce the potential heat release contained within the reactor volume, by reducing the inventory of reactive species. The reduced chemical inventory greatly reduces the severity of failure and also allows for a rapid emergency quench of the entire reactor contents in the case of potential runaway reaction. The improved heat transfer rates of continuous reactors also help to reduce safety concerns when scaling exothermic reactions. This characteristic results in dramatically improved temperature control and enables operation within a safe operating window. In some cases, continuous processing may be the only practical means of scaling a highly exothermic process. Some examples employing continuous processing to mitigate safety concerns are given below.

Many pharmaceutical syntheses involve reactions with short half-lives and high heats of reaction, and thereby pose thermal runaway potential. Some examples include nitrations, oxidations, and other reactions involving energetic compounds such as peroxides, azides, and diazo compounds [3, 4]. Nitrations are highly exothermic, involve explosive or hazardous nitrating agents, and continuous processes have been developed to implement this chemistry more safely. In one example, the nitration of a pharmaceutical intermediate utilized a continuous reactor to enable high chemoselectivity while mitigating temperature control and decomposition concerns that existed in the batch process [4]. The continuous process operated at 90°C with a 35 min residence time in a microreactor. In contrast, the batch process operated for 8 h at 50°C and required very precise addition control for nitrating reagents.

23.2.2 Product Quality

The selectivity of organic reactions is determined by the amount of time molecules are exposed to a given set of conditions, that is, stoichiometry and temperature. In batch processing, spacial gradients exist for temperature and reactant concentration due to the mixing times achievable with conventional batch reactors. Restated, in batch reactors, the reaction conditions vary with location in the reactor. That nonuniform reaction environment can lead to undesirable side products and the extent of their formation depends upon the mixing characteristics of the reactor and the rate laws for both desired and undesired reactions. The increased heat and mass transfer capability of continuous reactors can result in improved reaction impurity profiles since conditions can be controlled more uniformly than with batch reactors. Improvements in impurity profiles at the reaction stage lessen the burden of downstream unit operations designed to remove impurities. This can allow for yield improvements due to optimization of downstream workup and crystallization. The improved control of reaction conditions should also help to minimize batch-to-batch variability that sometimes exists with batch processes.

There are additional consequences of the inferior heat and mass transfer properties of conventional batch reactors. Often reagents must be added over extended periods of time, and this means that there is a wide distribution in the amount of time that substrate molecules, starting material or product, are exposed to reaction conditions. While this increases cycle times, it also affects product quality and choice of operating conditions. These temporal gradients necessitate that conditions are defined to accommodate those molecules exposed to process conditions for the longest periods of time. Mean residence times are reduced in continuous reactors and molecules experience reaction conditions for more uniform periods of time. Additionally, the increased heat and mass transfer rates also mean that reaction conditions can be manipulated more rapidly than with batch reactors. The minimization of temporal gradients, coupled with the ability to rapidly manipulate reaction conditions, allows the process development engineer to consider operating conditions that would lead to unacceptable impurity profiles in batch processes. One example of this benefit is in the case where a relatively unstable intermediate is produced. Consider the time-temperature stability envelope displayed for a hypothetical first-order decomposition in Figure 23.1. The stability of a chemical intermediate increases at lower temperature, decreases with time, and these parameters are coupled. This fact means that batch reactions requiring low temperatures and long reaction times for stability reasons can possibly be converted to high temperature continuous processes when operated for a much shorter period of time. This same concept applies to all reactions, desired and undesired, and by understanding the rate laws governing them, continuous processing conditions that improve reaction selectivity can often be identified.

Many examples exist where continuous processing led to improved product quality [5, 6]. For example, the biphasic BOC-protection of an amine was investigated with continuous flow reactors due to its high heat of reaction, −213 kJ/mol, and the propensity to form dimeric impurities [5]. The dimeric impurities were reduced and the overall selectivity was improved from 97% to 99.9% in the continuous process. The improvements were attributed to the

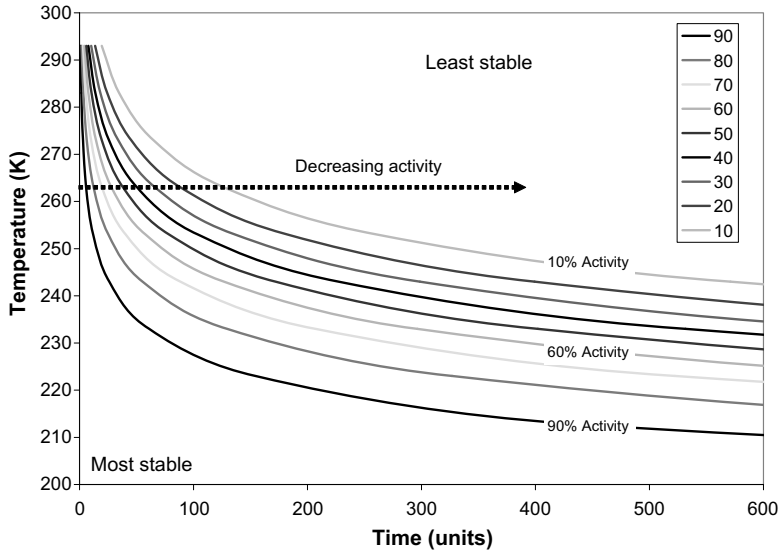

FIGURE 23.1 Operating chemistry envelope for a hypothetical first order degradation mechanism. The stability (activity) of an intermediate is a function of time and temperature. The rate of degradation increases with higher temperatures.

reduction of spacial and temporal gradients in reaction conditions.

23.3 CONTINUOUS REACTOR AND ANCILLARY SYSTEMS CONSIDERATIONS

The three main components of a continuous reaction process include the feed solutions, the reactor, and the quench [7] (Figure 23.2). We will first consider the reactor followed by the ancillary systems for the feed solutions and quench.

23.3.1 Continuous Reactors

23.3.1.1 Plug Flow Reactors Ideal plug flow reactors (PFRs) have flow with minimal back mixing along the flow path, no radial concentration or temperature gradients and a precise residence time for all flowing material. In the case of

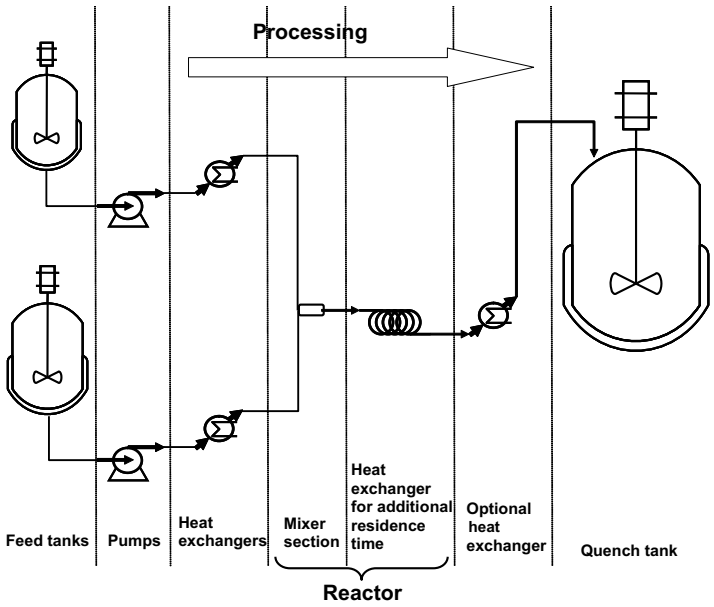

FIGURE 23.2 Typical continuous processing scheme.

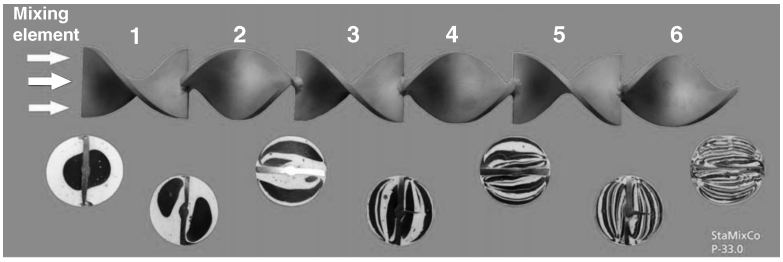

FIGURE 23.3 Cartoon demonstrating operating principle of a static mixer. Courtesy of StaMixCo LLC.

laminar flow, radial gradients may exist and there may not be plug flow in the truest sense. However, for the rest of this chapter, the term plug flow reactor will refer to all tubular flow reactors, regardless of the degree of turbulence and radial gradients. Plug flow reactors are composed of mixing zones for mass transfer and heat exchangers for heat transfer, and often these components are present in a single device. The static mixers and heat exchangers commonly utilized for these purposes in the pharmaceutical industry are described below and can be used in any combination required to meet the demands of the particular process.

In-line static mixers are commonly utilized in plug flow reactor systems to efficiently mix multiple feed streams. Tubular static mixers have characteristic mixing times of a few seconds or less depending on the degree of turbulence and provide efficient mixing even in the case of laminar flow. Static mixers consist of sequential static, often helical, mixing elements housed in a tube. The mixing elements typically alternate between left and right handed torsion and simultaneously produce flow division and efficient radial mixing, minimizing radial gradients in velocity, temperature, and concentration. A cartoon demonstrating the operating concept of a static mixer is given in Figure 23.3. In the case of the common Kenics® static mixer, each mixing element divides the process fluid in half. Each fluid division is further divided by subsequent mixing elements and the number of fluid striations is theoretically equal to 2^N, where N is the number of individual elements. In this simple way, miscible fluids can be thoroughly mixed within a very short length of tubing, even under laminar flow conditions. Selection of the mixing inserts and number of elements depends on the fluid properties and the specific processing application [8]. A variety of vendors (Kenics, Komax, Sulzer, etc.) manufacture static mixers and can aid in the selection of the most appropriate mixing elements. Static mixers are typically jacketed to control temperature when used as a reactor, and in one example, the mixing elements are made of heat transfer tubes for improved temperature control [9]. Figure 23.4 shows an example of a lab static mixer where 27 helical mixing elements are contained within 7 in. of 1/4 in. tubing, equating to a theoretical 134 million striations. Static mixers offer advantages over mechanical agitators such as more rapid mixing, ease of maintenance, and lower operating costs.

Heat removal and temperature control in plug flow reactors are achieved with heat exchangers. The versatility of heat exchangers is demonstrated in the case studies of the latter sections of this chapter, where heat exchangers are utilized to adjust the temperature of feedstocks prior to reaction, to control the temperature in the mixing zone of the reactor, to provide additional residence time for complete conversion of the reaction, and to thermally quench reactions. They are an essential component of plug flow systems. The key advantage of heat exchangers, versus conventional stirred tanks, is their improved heat transfer rates that result from much higher surface area to volume ratios. Most commonly used by the authors are concentric tube and shell and tube heat exchangers that are readily available from vendors and easily constructed in house as well. Schematics of several variants of these are shown in Figure 23.5. These heat exchangers are readily available at low prices, have reasonable pressure drops, and meet the heat transfer requirements for most reactions. By inserting mixing elements into one of these heat exchangers (Figure 23.5), a PFR can be constructed that provides good heat and mass transfer. Due to the simplicity of construction and lack of moving parts and

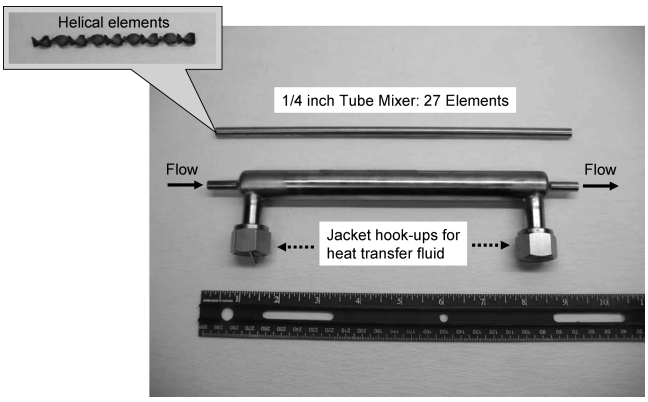

FIGURE 23.4 1/4 in. tube mixer with 27 elements and a 1/2 in. jacket for added temperature control.

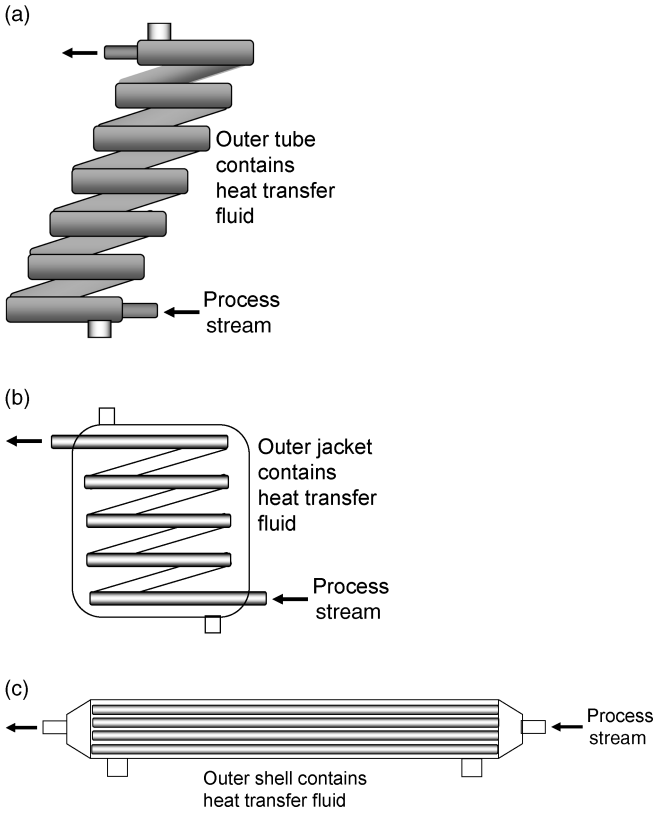

FIGURE 23.5 Heat exchangers commonly employed in continuous processing: (a) concentric tube, (b) jacketed coil, (c) shell and tube.

associated seals, a PFR provides a cost efficient reactor that is easy to construct and operate. Although they have better heat transfer properties than batch tank reactors, PFRs often operate nonisothermally for exothermic reactions.

23.3.1.2 Microreactors Microreactors are another type of flow reactor that have been increasingly studied and applied as laboratory tools for process screening and scale-up studies. The term microreactor typically implies a single unit integrating a static micromixer and heat exchanger combined with an additional heat exchanger that provides time for reaction conversion beyond the mixing zone. Other more specialized reactors such as spinning tube-in-tube [10] and spinning disk reactors [11] are less wide spread and will not be discussed here. Laboratory microreactors fabricated by glass or metals are available with an internal volume of less than 1 mL. As an example, a standard microreactor from Micronit Microfluidics [12] includes a preheating section for each input stream, a mixing section, and a quenching section from a third input. The total volume of this borosilicate reactor is 3.4 mL of which the mixing zone is 2.4 mL.

Microreactors are suitable tools to employ with fast reactions that require extremely efficient mixing and the reaction requires only low flow rates. Micromixers have internal microchannels that typically lie in the range of 50–500 μm. In these microfluidic devices, molecular diffusion is the governing mixing mechanism within the laminar flow domain, unlike turbulent mixing created in a pipe or mechanically agitated vessels. Many micromixers can maximize the interfacial surface contact of fluid lamination and efficiently minimize concentration gradients. The internal microstructures promote multiple flow divisions and recombinations and are designed for specific flow arrangements and fluid types [13]. For example, T-mixers and interdigital mixers (Figure 23.6) are routinely used in microreactors for obtaining efficient liquid–liquid mixing. Microreactors also possess extremely high surface to volume ratios for enhanced heat transfer and can therefore operate isothermally even with exothermic reactions. This expands processing

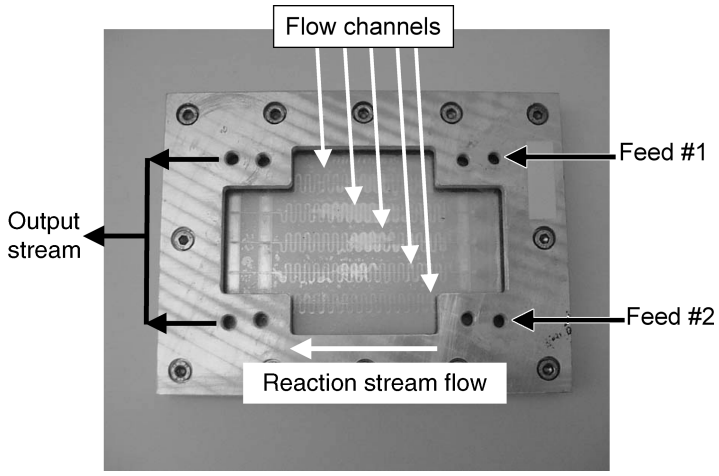

FIGURE 23.6 Microreactor from Mikroglas Chemtech GmbH: interdigital mixer with heat exchanger, five channels with a width of 500 μm and a depth of 250 μm.

opportunities for managing hazardous or highly energetic chemistries with enhanced safety.

23.3.1.3 Continuous Stirred Tank Reactors Continuous stirred tank reactors (CSTRs) are presented last because they are less commonly used in the pharmaceutical industry. They are essentially batch tank reactors that are operated continuously by simultaneously flowing reactants in and product out. Since they are tank reactors, their heat and mass transfer characteristics are equivalent to similarly sized batch tank reactors. Additionally, single CSTRs have broad residence time distributions and low conversion rates per unit volume. Some of these characteristics of CSTRs can be improved by using a series of smaller reactors cascaded together as shown in Figure 23.7. CSTRs cascaded in this way have been used for several processes at AMPAC Fine Chemicals LLC for the production of hazardous or energetic chemicals [14]. In one facility, they utilize up to seven cascaded reactors from 0.25 to 1 L in volume for a continuous process [15].

23.3.2 Choosing Between CSTRs, PFRs, and Microreactors

As demonstrated earlier, continuous processes have the potential to deliver higher throughput, improved heat and mass transfer, and improved impurity profile through control of precise reaction conditions. The ability of the continuous process to deliver on this potential largely depends on the type and size of reactor chosen. In this section, we will make some general comparisons between PFRs, microreactors, and CSTRs. A qualitative comparison of key attributes for these reactors is given in Table 23.1. The case will be made that PFRs and microreactors are generally preferred over CSTRs. PFRs are preferred over microreactors when they are capable of meeting the heat and mass transfer demands of the reaction of interest.

As shown in Table 23.2, reactions can be grouped into three general kinetic categories: (1) very fast with a half-life of less than 1 s, (2) rapid reactions, typically 1 s to 10 min, and (3) slow reactions greater than 10 min. The rate of heat and mass transfer required by the process varies between these categories and in large part determines the choice of reactor. Since the rate of reaction depends upon the conditions chosen, it is sometimes possible for categorization of a reaction to change based upon reaction conditions.

The mass transfer requirements for a reaction depends upon the reaction categorization. For reactions with a half-life less than 1 s, microreactors may be the only practical choice due to mass transfer limitations of PFRs, and especially CSTRs. Even though static mixers can greatly enhance mixing in PFRs, they pail in comparison to the millisecond mixing times that are characteristics of micromixers. The degree to which PFRs may be acceptable for these reactions depends in part on the extent to which concentration gradients influence reaction selectivity. Reactions in the second category have less stringent mass transfer requirements. With PFRs or microreactors, they are likely kinetically controlled, but concentration gradients may influence selectivity if conducted in CSTRs. Reactions in the third category have even less stringent mass transfer requirements and either PFRs and CSTRs may be appropriate depending upon specific process needs.

Another major factor in reactor selection is heat transfer requirements of the process. Since the heat generated by a reaction is proportional to reactor volume and the heat removal is proportional to reactor surface area, the ratio of surface area to volume provides an easy means of comparing a reactor's ability to remove heat. Table 23.3 shows this ratio for a 2000 L batch reactor compared to a smaller CSTR, tubular PFR, and a system of microreactors capable of similar throughputs. Obviously conversion of an existing batch reactor to a CSTR does nothing to improve the heat transfer characteristics. Although a smaller CSTR represents a great

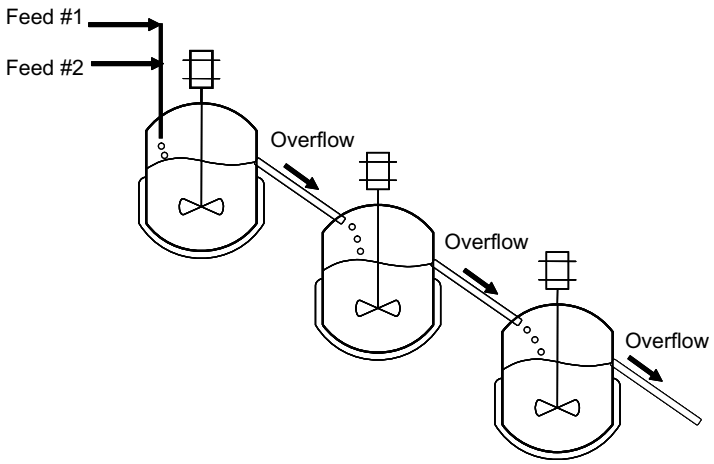

FIGURE 23.7 Cascaded continuous stirred tank reactors in series.

TABLE 23.1 Attributes of CSTRs, PFR and Microreactors

Reactor Mode	Multiple CSTRs	PFR	Multiple Microreactors
Handling of solids	+ +	−	− −
Gas evolution	+ +	−	− −
Slow reaction kinetics	+ +	−	− −
Quickly achieve steady state	−	+ +	+ +
High conversions per volume	−	+ +	+ +
Narrow residence time distribution	−	+ +	+ +
Mitigates product reacting with starting material	−	+ +	+ +
Initial large heat sink	+	−	−
Low operational complexity	−	+ +	− −
Low level of equipment intensity	+	+ +	− −
Enhanced heat transfer	−	+	+ +
Enhanced mass transfer	−	+	+ +
Low cost	+	+	− −

+ +: strong positive characteristic; +: positive characteristic; − −: strong negative characteristic; −: negative characteristic.

TABLE 23.2 Categorization of Reactions for Continuous Process Fit [16]

	Reaction Rate	Characteristics
1	Very fast	Reaction half-life of less than 1 s. Reaction is mixing sensitive since rate is faster than mixing. Most of the reaction occurs in the mixing stage for a continuous reaction. Heat management can be an issue
2	Rapid	Reaction half-life is 1 s to 10 min. Reaction may be mixing sensitive, but typically kinetically controlled. Heat management may be an issue
3	Slow	Reaction half-life greater than 10 min. Implemented in a continuous process mainly for hazardous chemistries

improvement over batch reactors in terms of surface to volume ratios, it cannot compete with tubular PFRs or integrated microreactors. Reactions in category 1 are often highly energetic and the rapid generation of heat may require a microreactor if a high degree of temperature control is required. PFRs however meet the heat removal requirements of many common reactions, and can be used for more energetic reactions if nonisothermal operation is acceptable. The nonisothermal characterization refers primarily to temperature gradients in the axial rather than radial direction.

In order to realize all of the benefits described earlier, a narrow residence time distribution is often required. For an ideal PFR, all molecules have the same residence time and the distribution is represented by a Dirac delta function. While real PFRs are less perfect, they have very narrow residence time distributions. Microreactors operate in laminar flow and axial dispersion models have been used to model the residence time distribution [17]. This deviation from ideal plug flow is less important for microreactors since they are typically operated with shorter mean residence times, and it is the absolute value of the residence time at the upper boundary of the distribution that impacts impurity profiles, not the percent deviation. CSTRs have a broad residence time distribution and some molecules spend considerably longer in the reactor than others. In fact, the standard deviation of the CSTR residence time distribution is equal to the mean residence time. For processes requiring exposure to reaction conditions for a precise period of time, PFRs are preferred. Furthermore, the residence time distribution in CSTRs results in longer transient periods, typically three to four residence times, prior to reaching steady state. The longer transient periods for CSTRs result in larger amounts of wasted product and are an additional drawback of CSTRs.

TABLE 23.3 The High Surface Area to Volume Ratios for Continuous Reactors are Due to the Small Characteristic Reactor Dimension

Reactor	Characteristic Dimension (mm)	Surface Area/ Volume (cm^{-1})
2000 L tank	680	2.9×10^{-2}
50 L CSTR	200	0.10
Tubular PFR (500 mL)	3.2	3.1
Microreactor[a]	0.05	400

[a] 50 + units would be needed to meet throughput requirements.

For processes that are not constrained by heat and mass transfer or residence time distribution considerations,

throughput considerations may be important when choosing between CSTRs or PFRs. Continuous reactors will always offer a higher throughput than batch processing. Conceptually this is quite simple since in continuous processing reactants are constantly fed to the reaction and reactors operate at a constant volume, usually full. For positive order reactions with simple kinetic rate laws, the design equations for CSTRs and PFRs dictate that PFRs deliver a given conversion with smaller reactor volumes than CSTRs. The extent of divergence between CSTR and PFR volume depends upon the rate law and the conversion required in the reaction, and it is especially pronounced when high conversions are required. Conversions in the pharmaceutical industry are nearly always greater than 95% and quite frequently are greater than 99%. Table 23.4 compares the CSTR reactor volume, relative to a PFR, required for a first- or second-order reaction to achieve 99% conversion. For a single CSTR to reach 99% for a second-order reaction, it would need to be 100 times larger than its PFR counter part. The conversion efficiency of CSTRs is improved by cascading several in series, and in the limit of an infinite number of CSTRs in series performance equals that of a PFR. Based upon conversion, or throughput per unit volume, PFRs are clearly superior to CSTRs.

Considerations for ease of operation and reactor costs may factor into choice of reactor as well. Based upon the authors' experience, PFRs represent a good balance between cost, heat, and mass transfer efficiency, and ease of operation, and they are preferred when they meet the demands of the process. To the extent possible, attempts are made to modify reaction conditions to allow the use of PFRs. While microreactors have superior heat and mass transfer rates they are significantly more expensive than PFRs due to the fine machining required to construct their microchannel flow paths. PFRs on the other hand are simple jacketed tubes with mixing elements and their cost reflects this simplicity. Another practical drawback of microreactors is their relative inability to handle even small amounts of solids. Individual particles may be sufficient to block flow and interrupt operation. By comparison, the larger diameters of most PFRs allows slurries with low solids density to flow. Slurries with higher solids loading likely require CSTRs for operation, or may not lend themselves to continuous processing at all. Additionally, CSTRs can be better suited for handling reactions that involve large amounts of gas evolution. In microreactors, generation of large amounts of gas can serve to reduce the residence time by forcing the process stream through the reactor more rapidly than intended. Non-CSTR reactors can be designed to handle gases and one of the authors has developed and implemented a continuous trickle bed oxidation column for production of a pharmaceutical intermediate [18]. A final instance where CSTRs might be preferred is the case of slower reactions requiring longer residence times for complete conversions. In such circumstances, the length of a PFR required to accommodate the longer residence time may result in impractical pressure drops.

TABLE 23.4 Comparison of Reactor Volume for Multiple Stirred Tank Reactors in Series Versus a Plug Flow Reactor Based on 99% Conversion of Starting Material

# of Stirred Tank Reactors in Series	Volume Relative to a Plug Flow Reactor	
	First-Order Kinetics	Second-Order Kinetics
1	22	100
2	4	8
3	2.4	4
4	1.8	2.6
6	1.5	2
∞	1	1

23.3.3 Ancillary Systems

23.3.3.1 Feed Solutions All of the reactants for a continuous process must be in a form that is easily transported by pumps or pressure transfer. Since a higher number of feed solutions requires a proportional number of tanks and feed control systems it is generally desirable to combine several solvents and reactants when possible. Of course, species that react with one another should be prepared in separate feed streams. Typically, one feed solution will contain the starting material and the bulk solvent while a second feed contains the reagent. In some cases, a third feed may contain a second reagent, a catalyst, or possibly a second compound in the case of a coupling reaction. Ideally, the feed solutions should be homogeneous to avoid reactor plugging or fouling, and knowledge of substrate solubility in all process streams is desirable. Additionally, knowledge of the chemical stability of each feedstock is imperative for successful operation.

23.3.3.2 Quench The quench brings the reaction mixture to a nonreactive and stable condition for downstream processing. The quench can be chemical or thermal in nature and the choice depends on the reactivity of the processing stream and downstream processing needs. Examples of both are given in the two case studies sections. The three predominant quench modes utilized in continuous processing are demonstrated in Figure 23.8. While these modes are depicted for chemical quenches, slight variants can be envisioned for thermal quenches as well. The first is a reverse batch quench where the reaction stream flows into a reactor containing the quench material. Depending upon processing needs, parallel quench vessels can be setup to alternately receive the continuous reaction stream and allow uninterrupted operation of the reactor. Under this scenario, the contents of the off-line

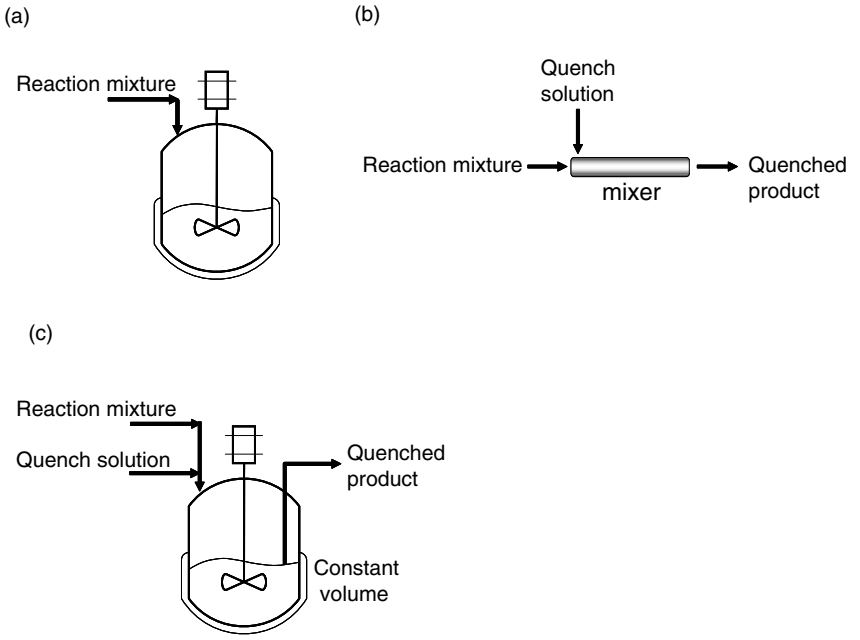

FIGURE 23.8 Continuous reaction stream quench scenarios. (a) Reverse quench; (b) continuous quench with in-line mixer; (c) continuous quench with CSTR.

quench tank are worked up, while the second quench tank continues to receive the reaction stream. This operating mode is the least complex, ensures an excess of quench solution, may provide a good heat sink for exothermic quenches, and provides a well-defined delineation of batches from a GMP perspective. The second mode of quenching utilizes a static mixer, typically jacketed, to introduce the quench solution. Assuming downstream processing is conducted batchwise, the quenched solution would be collected in stirred tank reactors. The third mode of quenching is similar to the second, but uses a CSTR for the continuous quench. Since this quench mode would require an additional reactor as a collection vessel, it is relatively impractical unless subsequent processing is conducted continuously.

23.4 PROCESS DEVELOPMENT OF THE CONTINUOUS REACTION

23.4.1 Reaction kinetics

A prerequisite to designing a continuous process is to understand the rate laws governing the kinetics of the desired and undesired reactions. The level of knowledge required depends upon the complexity of the process, but where possible a complex reaction should be broken down into its elementary reaction steps and the rate laws for each step established. In some cases, the development of an overall apparent rate law may be sufficient. In either case, the activation energy, and effects of reactant concentration should be established for both desired and undesired reactions. It should be noted that the kinetic experiments need not be conducted in a continuous reactor since the reaction kinetics do not depend upon mode of operation. However, in some instances such as fast reactions, flow reactors may offer a practical means of studying reaction rates. With rate laws established, an overall kinetic model can be constructed to help identify operating conditions—temperature, concentration, and time—that promote high rates of conversion and selectivity toward the desired product. In this way, the process development engineer can realize the full potential of the improved heat and mass transfer rates and precise residence times of plug flow reactors and microreactors.

EXAMPLE 23.1

Show how residence time varies with conversion in a PFR for a constant-density first-order reaction. Generate a table of conversion versus residence time. Assume the first-order rate constant is $0.01\ s^{-1}$. Compare the residence times required to reach 90% conversion, 99%, 99.9%, and 99.99%.

Starting with the design equation for a PFR:

$$\frac{V}{F_{A0}} = \int_0^X \frac{dX}{-r_A} \tag{23.1}$$

Substituting the rate equation

$$-r_A = kC_A \tag{23.2}$$

$$C_A = C_{A0}(1-X) \tag{23.3}$$

$$\frac{V}{F_{A0}} = \frac{1}{kC_{A0}} \int_0^X \frac{dX}{1-X} \tag{23.4}$$

where F_{A0} is the entering molar flow rate and C_{A0} is the initial molar concentration.

Integrate and substitute the residence time, τ, relation to obtain

$$\tau = \frac{VC_{A0}}{F_{A0}} = -\frac{1}{k}\ln(1-X) \tag{23.5}$$

Create a table for X versus τ using $k = 0.01\ s^{-1}$.

Thus, the residence time required to achieve 90% conversion is 230.3 s. It takes another 230 s to convert from 90% to 99% and another 230 s to convert from 99% to 99.9%, and so on.

23.4.2 Reaction Engineering

In addition to the kinetics, an understanding of the heat generated by the process needs to be understood in order to design an appropriate reactor for the process. The two main sources of heat generation are the heat of mixing and heat of reaction. The heat of mixing refers to heat generated upon mixing of the feed streams, including heats of dilution. The heat of reaction is proportional to reaction conversion and is distributed across the length of the plug flow reactor based upon the extent of conversion. For PFRs and microreactors, the bulk of the heat is generated in the first part of the reactor, and may primarily be in the mixing stage. This is in part due to the localization of the heat of mixing, but is primarily due to the distribution of reaction conversion, and thus heat, in the axial direction. For a first-order reaction in an isothermal PFR, the length of reactor required to reach 90% conversion is the same length required to go from 90% to 99% conversion. The first half of the reactor would need to dissipate an order of magnitude more heat than the second half. The amount of heat generated in the early part of the reactor is even greater for higher order reactions and in nonisothermal operation where the heat of reaction increases the temperature of the process stream early in the reactor, thus increasing the reaction rate and heat generated. It is therefore important to understand the intended reactor's overall heat transfer coefficient, or to design a reactor that meets the process's requirements.

Combining the kinetic rate laws, heats of reaction, and knowledge of the reactor's heat transfer coefficients provides a powerful means to model expected outcomes. A combined experimental and modeling approach is essential for rapid process development since so many parameters depend on one another. Figure 23.9 shows a generic workflow for

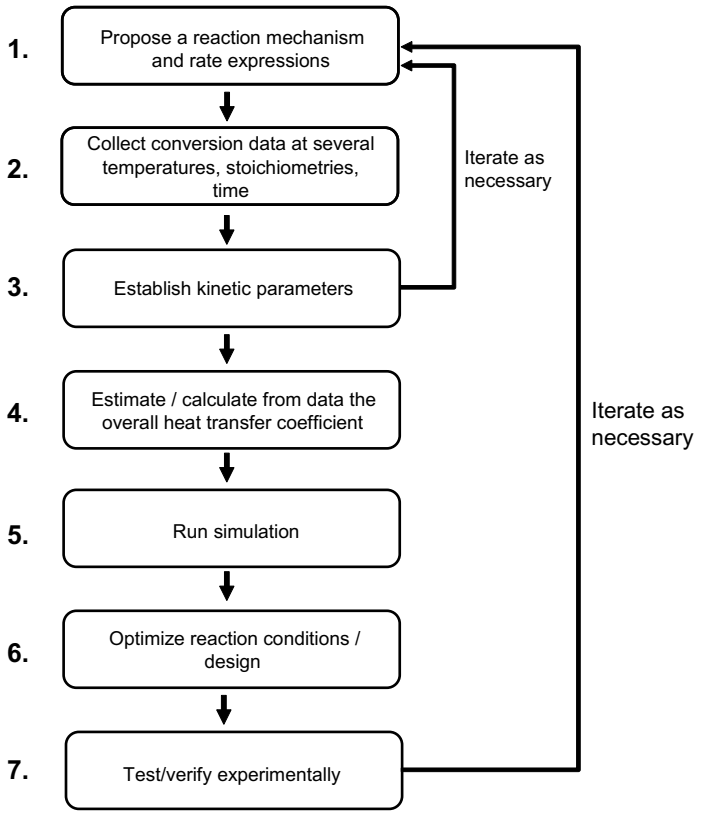

FIGURE 23.9 Workflow for process modeling.

continuous reaction development from a reaction engineering perspective. An understanding of the factors influencing heat generation is established in steps 1 through 3 by combining the kinetic rate laws and heats of reaction. The reactor's heat transfer properties and ability to remove heat are established in step 4. Simulations can then be conducted to determine reaction conditions at different positions along the reactor and ultimately product quality. Such simulations can be used to evaluate different reactor types and configurations, as well as changes in flow rates, stoichiometry, and temperature. With a good model, much of the process development can be facilitated by virtual experiments. The final step is to experimentally verify the optimized conditions, or redesign the reactor.

Examples of this type of methodology exist in the literature [3, 19] and an example is also given in the case studies section of this chapter. Bogaert-Alvarez et al. [3] undertook a good example of this approach. They solved the rate laws and nonisothermal heat transfer equations as two ordinary differential equations for a plug flow reactor. They assumed a constant temperature for the heat transfer medium although an energy balance of it could also be included. The model enabled them to evaluate the effects of various parameters including jacket temperature, reactor length, flow rate, and heat transfer coefficients on reaction conversion and peak reaction stream temperatures.

As discussed earlier, microreactors and PFRs can combine any number of mixing zones and heat exchangers to accommodate the needs of a process. Combining this flexibility with the predictive models described earlier can lead to improved reactor design and influence conversion rates and product quality. Since the reactant and product concentrations vary along the length of the reactor, different stages may benefit from different operating temperatures. In the case of moderately or highly exothermic reactions, the reaction temperature may spike above the desired control point during the initial portion of the reactor (Figure 23.10a). Because the greatest amount of heat is generated at the entrance of the plug flow reactor, a two-zone jacket temperature may facilitate greater reaction temperature control (Figure 23.10b). In this example, the two zones consist of a lower initial jacket temperature of 63°C versus the 80°C on the remaining portion of the reactor. Alternatively higher temperatures can be utilized later in the reactor to improve conversion rates. Similarly reactors can be easily designed to accommodate multiple feed points at different stages along the reactor to further manipulate reaction conditions if required. In this way reactors can be specifically designed for maximum throughput and product quality.

While the reaction engineering discussion thus far has focused on product quality, the same concepts can be utilized for process safety evaluations. Since most of the reactions employed in the pharmaceutical industry are exothermic, this safety aspect is an important consideration. This is especially true of nonisothermal PFR operation where rates of heat generation and temperature vary along the length of the reactor. Reactions should be evaluated in combination with proposed reaction conditions to avoid potential runaway reactions and ensure a sufficiently large safe operating window.

23.5 SCALE-UP: VOLUMETRIC VERSUS NUMBERING-UP

Classical scale-up of a batch process consists of increasing the volume of the batch reactor. As a result of poorer heat and mass transfer in larger reactors, many of the common operations of batch processing take significantly longer at larger scales. Activities that frequently take longer at scale are charging of reagents, batch heat-up or cool-down, and reaction quench. The improved heat and mass transfer capabilities of continuous reactors means that lab- and plant-scale processing times are much better aligned. For example, the reaction time does not change with scale since it is the design criterion for the continuous process. Additionally, the reaction stream is quenched immediately upon completion of the reaction at any scale.

Scale-up of most continuous processes occurs by increasing the total reactor volume and the flow rate to maintain the same residence time established during development. However, an alternative approach in continuous processing scale-up, particularly for using microreactors, is to number up. Here the reactor system is duplicated numerous times, with all running in parallel [20]. At DSM, multiple parallel microreactors were utilized for pilot-scale production of a nitration reaction of a pharmaceutical intermediate [21]. In this scenario, the replication of the same geometries and flow rates for each unit provides the higher overall process flow rates, and thus avoids any scale-up effects. The logistics, complexity, and capital investment of such systems may limit widespread implementation for high-volume products. Examples where processes have been numbered up using microreactors for commercial manufacturing are rare and this approach may not be amenable for most processes without additional technological advances particularly in automated flow stream division and control.

LaPorte et al. [18] demonstrated a less intensive example of numbering-up of a gas–liquid reaction. They replicated a trickle bed column and housed the set of four in a common baffled jacketed tube for temperature control. An enolate stream was split equally into four streams using rotameters and each stream flowed into one of four trickle bed columns. This scale-up facilitated a $4\times$ numbering-up by maintaining the same fluid dynamics, mass transfer and heat transfer characteristics in each tube. This operation did require constant monitoring since the flow splitting was not

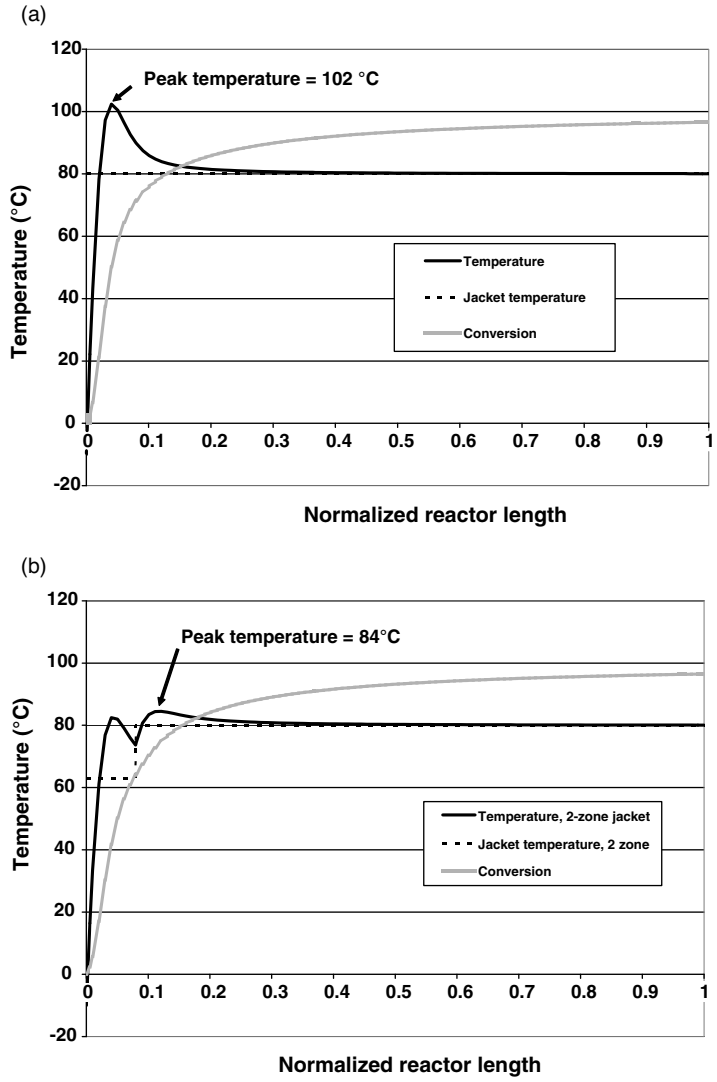

FIGURE 23.10 Simulated reaction temperature profile for a second-order reaction in a plug flow reactor. A constant jacket temperature is assumed for a single jacket temperature zone (a) and a two-zone jacket (b).

automated. Commercial processes would require a high degree of automation to ensure the proper flow at all times. Other approaches to scale-up, particularly for a microreactor, include adding to the volume of the reactor with serial addition of reactor plates. Hence, a large range of flow rates from milliliters to several hundred milliliters per minute is possible for a specific reactor platform [22].

23.6 PLANT OPERATIONS

23.6.1 Flow Control

Flow control is a critical parameter for a continuous process. The total flow of the streams ensures the proper residence time for reaction, and the ratio of the individual streams ensures the proper stoichiometry of the reagents. The feed streams must be accurate and consistent, and the constraints on those parameters depend on the tolerance of the process. One approach to minimize pulsating flows is to utilize pressured feed tanks along with flow meters and control valves to control the flow rate. Another possibility is to use metering pumps for each of the feed streams. For pumps that pulsate (piston, diaphragm, etc.), synchronization, dampening devices or multiple pistons that are sequenced and positioned on one pump may be required. Pulseless pumps with an integrated mass flow meter and feedback control system are ideal. These systems provide precise metering for processes with tight flow tolerances.

23.6.2 Process Analytical Technology

Process analytical technology (PAT) is an important part of most continuous processes as it provides a useful means of monitoring the state of the reaction. Indeed, one of the stated goals of the FDA's PAT initiative is "Facilitating continuous processing to improve efficiency and manage variability" [23]. Typical PAT tools include Raman, FTIR, NIR, and UV-Vis spectroscopy [24, 25] or other noninvasive monitoring techniques that can be adapted to a flow cell or tube reactor. These tools can be used during both transient and steady-state operations. As an example, FTIR was used to determine the proper ratio of reagent feed rate to starting material feed rate during the start-up of a continuous process to make an active pharmaceutical ingredient [18]. For this particular process, the same PAT equipment could have been used to monitor the product quality. In a well-defined continuous process it is envisioned that feedback controllers could adjust operating parameters based on input signals from PAT analyzers. Even in the absence of feedback control, PAT can provide valuable information to plant operators who can modify the operation if necessary. If PAT analyzers indicate that product quality is suspect, flow can be diverted to alternative holding tanks for further analysis. In the absence of spectroscopic analyzers, simple temperature measurements at various reactor positions can provide a wealth of information regarding reaction performance.

23.7 CASE STUDY: CONTINUOUS DEPROTECTION REACTION—LAB TO KILO LAB SCALE-UP

A batch process to carry out an acidolysis and deprotection chemistry for a pharmaceutical intermediate involved adding the substrate solution to triflouroacetic acid (TFA) at approximately 0°C. The complete reaction mixture was immediately quenched into a biphasic mixture of aqueous base and ethyl acetate. An amide impurity was formed at high levels of >2%. The longer quench times anticipated upon scale-up were expected to further increase the level of the amide impurity.

A continuous processing approach was undertaken to minimize impurity formation through improved control of reaction time and reduced quenching time. The continuous reaction was assessed in the laboratory by mixing two feed streams, one for the substrate and the other TFA, in a glass microreactor with an overall volume less than 10 mL. Experiments varying temperature and residence time identified process conditions, 25°C and a minimum residence time of 4 min, which provided complete conversion and a significantly lower level of amide impurity, approximately 1%.

The preliminary reaction kinetics obtained from the small-scale continuous reactions paved the way for a rapid process scale-up. A 100-fold increase in flow rate in the substrate and TFA streams was used to process approximately 5 kg of starting material using the setup shown in Figure 23.11. The starting material solution was not stable at room temperature and required storage at −10°C. A preconditioning heat exchanger was used to continuously heat up the starting material feed stream to the reaction temperature, 25°C, just prior to reaction. A PFR, constructed of a jacketed static mixer for mixing the two feeds and three sequential concentric tube heat exchangers, operated with an overall residence time of 5 min. The reaction stream was continuously quenched in a jacketed static mixer and the quenched mixture flowed into a receiver for subsequent processing. The use of a static mixer for the quench ensured effective mixing of the biphasic process stream while rapidly quenching the reactive species.

This particular batch process was relatively simple to convert to a continuous process. However, it is a good

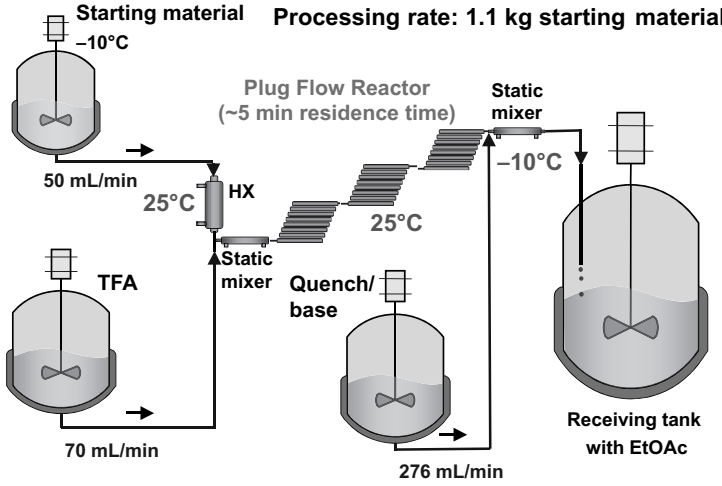

FIGURE 23.11 Kilo lab continuous flow setup for acidolysis and deprotection process.

example to demonstrate the key components and strategies behind the development process. This includes the use of stable feeds, preconditioning of a feed, and combined in-line jacketed static mixer and heat exchangers as the reactor.

23.8 CASE STUDY: CONTINUOUS PRODUCTION OF A CYCLOPROPONATING REAGENT

23.8.1 Introduction

The Simmons–Smith cyclopropanation is a well-known reaction to form cyclopropanes from olefins utilizing zinc and an alkyl iodide. The structure of the reactive zinc carbenoid species is the subject of numerous papers [26,27]. Formation of the active species is relatively exothermic with an adiabatic temperature rise above 120°C. Additionally, the complexes are known to be unstable for extended periods of time above 0°C. The exothermic nature of the reaction, combined with the complexity and incomplete understanding of the mechanism, and relative instability of the active species made scale-up very challenging in a batch process. One solution to the scale-up was the development of a continuous process for formation of the cyclopropanating reagent. The process was demonstrated at lab scale, scaled-up to pilot plant scale, and was used to make launch supplies for the starting material of a commercial API. The development and implementation of this process are discussed here.

23.8.2 Process Development

The strategy for developing a continuous process was to operate a PFR with a short residence time and higher temperatures, followed by a rapid thermal quench. A short reaction time was required to minimize the size of the plug flow reactor as well as reagent degradation. Initial screening work utilized a coiled 1/8 in. stainless steel jacketed tube as the reactor. Later in development, multiple 26 mL shell and tube heat exchangers containing up to 19 1/8 in. stainless steel tubes (Figure 23.12) were utilized. The heat exchangers were sequenced end to end to form the plug flow reactor. The reactor was operated with a short 50 s residence time. Due to the short residence time and the large amount of heat generated early in the reactor, isothermal operation was not possible. Details of the process are described below.

The laboratory setup used for development of the continuous process is shown in Figure 23.13. Two feed streams, one containing diethyl zinc (13.5 wt%) and dimethoxyethane in toluene and the other containing diiodomethane in dichloromethane, were held at ambient temperature. These streams were fed to the reactor with gear pumps and mass flow meters to ensure proper stoichiometry and residence time. Both streams passed through independent heat exchangers with a 30°C jacket temperature prior to mixing in a nonjacketed static mixer containing 27 helical mixing elements. The feeds entered the static mixer at about 29°C and exited at about 48°C. The reaction mixture flowed through a series of three shell and tube heat exchangers with 30°C jacket temperature to facilitate formation of the reagent. The process stream exit temperature was 52°C after the first heat exchanger and 32°C after the third. The 2°C temperature difference observed between process and jacket sides of the third heat exchanger indicates that the reaction was nearly complete by that stage. Additional calorimetric laboratory experiments that evaluated residual heat generation of the reaction mixture confirmed this observation. Finally, the reaction was thermally quenched to less than −10°C, again with a shell and tube heat exchanger. The process attained a steady state within three residence times based on multiple temperature measurements at various points along the plug flow reactor.

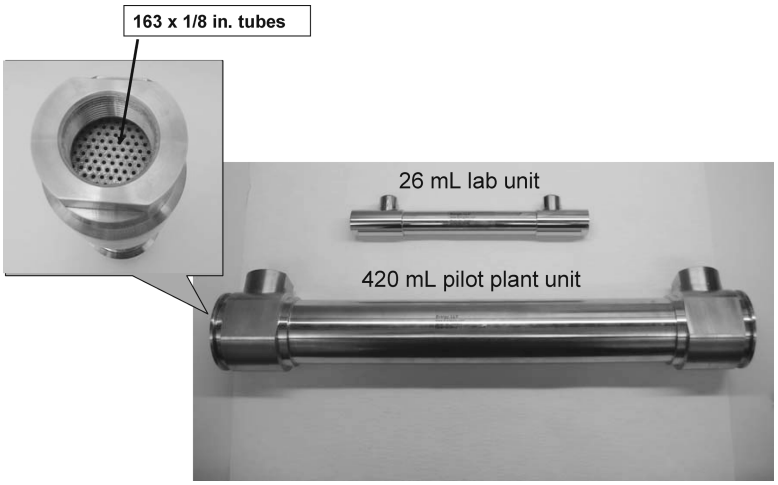

FIGURE 23.12 Mini shell and tube heat exchangers for laboratory or pilot plant use.

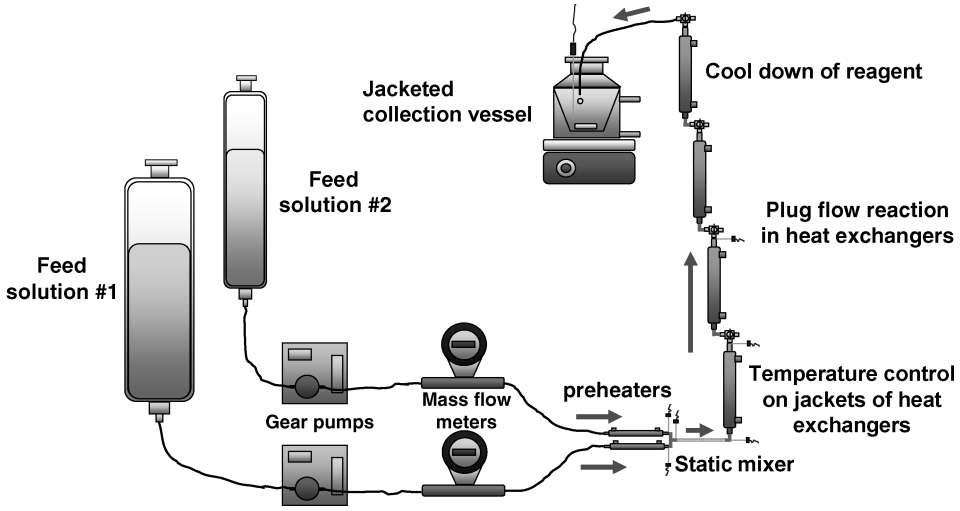

FIGURE 23.13 Laboratory setup for development of the Simmons–Smith reagent continuous process.

23.8.3 Modeling and Simulation

A reaction engineering approach similar to that described earlier was employed here to gain further insight into the continuous process. The proposed reactions for the model are formation of the Furukawa complex and Wittig complex and are shown in Figure 23.14. A proposed kinetic model and energy balance equation governing the reaction are shown as follows:

Nonisothermal plug flow reaction model

Assumptions:

- Completely mixed in radial direction
- No diffusion in flow direction (axial)
- Constant shell side temperature
- Constant stream density
- A two step reaction mechanism producing first the Furukawa complex followed by the Wittig complex
- Modeled on a per tube basis in the heat exchanger
- Overall heat transfer coefficient is independent of the number of tubes in the heat exchanger (constant shell side temperature)

Reaction Mechanism:

$$\mathrm{A} + \mathrm{B} \rightarrow \mathrm{F} \quad \Delta H_1 = -99\,\mathrm{kJ/mol} \tag{23.6}$$

$$\mathrm{F} + \mathrm{B} \rightarrow \mathrm{W} \quad \Delta H_2 = -94\,\mathrm{kJ/mol} \tag{23.7}$$

where A is the diethyl zinc/dimethoxyethane, B is the diiodomethane, F is the Furukawa complex, and W is the Wittig complex.

Rate Expressions:

$$k = A\,\mathrm{e}^{-E/RT} \tag{23.8}$$

$$r_1 = -k_1 C_\mathrm{A} C_\mathrm{B} \tag{23.9}$$

$$r_2 = -k_2 C_\mathrm{F} C_\mathrm{B} \tag{23.10}$$

Simplified Mass/Energy Balance:

$$u\rho C_\mathrm{p} \frac{dT}{dz} = \Delta H_1 r_1 + \Delta H_2 r_2 - UA_V(T - T_c) \tag{23.11}$$

where u is the reaction stream velocity, ρ is the reaction stream density, C_p is the reaction stream heat capacity, T is the reaction stream temperature, z is the axial position in plug flow reactor, ΔH_i is the heat of reaction, r_i is the rate of reaction, U is the overall heat transfer coefficient, A_V is the specific heat transfer area (area/unit volume), and T_c is the temperature of jacket coolant.

In this example, the reaction kinetics were not studied in separate detailed studies. Rather, the activation energies and frequency factors were fitted using the process stream temperatures at numerous reactor locations, a calculated overall heat transfer coefficient, and information on complex formation. Several assumptions were made in the modeling of

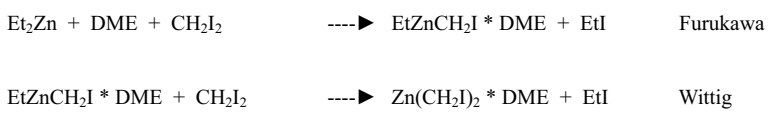

FIGURE 23.14 Modeled formation of complexes for the cyclopropanating reagent.

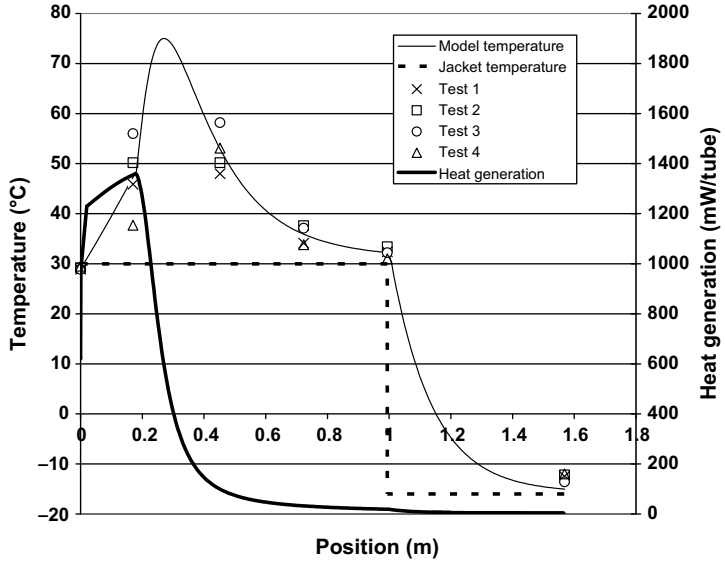

FIGURE 23.15 Test and model results for lab-scale plug flow reactor. Note that the axial velocity is higher in the static mixer due to a lower cross-sectional area relative to the heat exchangers. As a result, the shape of the temperature curve is influenced when plotted against position.

this process. Ideal plug flow was assumed although the Reynolds number was low and suggested laminar flow. The surface temperature of the heat exchanger tubes was assumed constant. Calorimetric studies provided the heat of reaction data. The kinetic model was fitted to the temperature profile with an estimated overall heat transfer coefficient [28]. Using the kinetic parameters, the reaction was simulated as it progressed through the reactor. Several local minima were determined during the model fitting exercise, requiring additional data to refine the model. The simulation results are shown in Figure 23.15, which plots temperature and heat generated versus axial position in the reactor. Although the residence time in the static mixer was only about 1.5 s, the maximum rate of heat generation was experienced there, at a reactor position of 0.18 m. As a consequence, the temperature of the reaction stream increased by 18°C since the static mixer was not jacketed. The static mixer could have been jacketed for additional temperature control, but it was not necessary in this case. The simulated reaction shows a maximum temperature of 75°C at about 0.27 m down the reactor. At this point, the heat generation is equal to the heat removal by the coolant flow. Although the predicted maximum temperature was not measured experimentally due to limited thermocouples in the PFR, the results seem reasonable and are consistent with the proposed reaction mechanism and experimental observations. The reaction reached 88% yield prior to being thermally quenched to less than −10°C for complex stability. Overall, the simulation does an adequate job in modeling the observed behavior and results from the laboratory. Despite limited knowledge of the reaction kinetics prior to modeling, the exercise demonstrates the utility of simulating a nonisothermal plug flow reactor. This type of process knowledge could be used to modify reaction conditions if necessary, but in this case was primarily used to guide the design and operation of pilot plant and commercial manufacturing reactors.

23.8.4 Process Scale-Up to Pilot Plant

With little additional development work, the process described in the previous sections was scaled up in a pilot plant to generate 700 kg of the cyclopropanating reagent solution. The feed tanks were pressurized and an actuated diaphragm valve coupled with a mass flow meter controlled the flow rate of each feed. The process was scaled by maintaining a similar residence time as in the laboratory, and essentially numbering up the laboratory setup by having a larger number of tubes in each heat exchanger, while maintaining the tube diameter. Unlike the batch process, this approach ensured similar heat and mass transfer characteristics and little change in reaction conditions when moving from the laboratory to the pilot plant. The PFR was constructed from a static mixer and five shell and tube heat exchangers, each containing 163 1/8 in. tubes. The total residence time was 65 s, similar to the 51 s residence time utilized in the laboratory. In the pilot plant, a spiral heat exchanger was used to facilitate the thermal quench. The design of the pilot plant system was otherwise similar to the previously described laboratory system.

Table 23.5 shows the different specifications for the laboratory and the pilot plant setups. The operation on pilot scale was similar to the laboratory process with slight differences in measured peak process temperatures most

TABLE 23.5 Laboratory to Pilot Plant PFR Specifications

	Laboratory	Pilot Plant
DME/DEZ (g/min)	70	1358
Diiodomethane/DCM (g/min)	48	940
Total mass flow rate (g/min)	118	2298
Volumetric flow rate (mL/min)	94	1868
PFR residence time (s)	50	65
Fluid velocity (cm/s)	1.7	3.85
Number of tubes (per shell)	19	163
Tube size (ID, cm)	0.254	0.254
Re number	53	120
Reactor length (m)	1.0	2.55
Heat load (W)	240	4700

likely due to differences in heat transfer characteristics. The maximum reaction stream temperature, measured after the first heat exchanger in the PFR, was 56–62°C. As a result, the PFR was operated with a higher jacket temperature relative to the laboratory reactor. After exiting the PFR, the reaction stream was thermally quenched and collected in a jacketed 2000 L reactor for later use. The process ran until all the feed solutions were consumed. The implemented continuous process facilitated production of 700 kg of reagent of consistent quality under reproducible conditions.

23.9 INTEGRATED CONTINUOUS PROCESSING IN PHARMA

While implementing continuous reactions can lead to improved safety and product quality, the increased manufacturing efficiencies experienced in the commodity chemical industry are largely unrealized when the downstream processing is conducted in a semi-batch fashion. This is a result of equipment downtime in such a scenario. Coupling multiple unit operations into a continuous process train has the potential to accelerate introduction of new drugs through more efficient production processes, and decrease the costs of production with smaller facilities, minimization of waste, lower energy consumption, and decreased raw material use [29]. Post-reaction processing in the pharmaceutical industry typically involves extractions, solvent exchanges, crystallizations, and drying and technologies currently exist to perform many of these unit operations continuously. For example, traditional chemical processing equipment such as Podbielniak centrifugal extractors, wiped film evaporators, and continuous crystallizers can perform extractions, solvent exchanges, and crystallizations continuously. These devices offer not only higher throughput but can also increase efficiencies as well, resulting in yield improvements and less waste. Additionally, parallel drying trains can be setup to alternately receive material from upstream continuous process trains. While integrated continuous processing of API is in its infancy, some companies have efforts underway [30] and others are collaborating with academia to develop new technologies for such purposes [2]. An integrated continuous processing plant may become more common in the pharmaceutical industry as technologies develop and as cost pressures rise. Whether these exist as smaller plants dedicated to a single product or modular multiproduct plants remains to be seen. Either way, the evolution will likely be slow given the entrenchment of existing batch processing plants and the real, or perceived, barriers to widespread acceptance of continuous processes.

23.10 BARRIERS TO IMPLEMENTATION OF CONTINUOUS PROCESSING IN PHARMA

The barriers to continuous processing in pharma are largely historical and involve GMP documentation concerns, lack of experience and understanding, and an existing infrastructure designed for batch processing. The pharmaceutical industry has traditionally preferred batch processing largely because of GMP documentation and traceability purposes. By having obviously defined discrete batches or lots of material it is straightforward to meet GMP requirements to document and verify the processing activities, parameters, and raw materials that go into each batch. Since continuous processes do not have well defined and frequent beginning and end points, there is a perception that the definition of a batch is less obvious. This is a misperception however, since the FDA's own guidance states "In the case of continuous production, a batch may correspond to a defined fraction of the production" [31]. Clearly, the FDA is willing to work with industry to adapt traditional GMP approaches to work with continuous processing. The prolonged absence of continuous processing in pharma has led to a dearth of continuous processing know how, both in development and manufacturing. That barrier has largely been reduced, especially on the development side, over the last decade as the regulatory hurdles to continuous processing have lessened and chemical engineers bring their skill sets to bear on the industry. With regulatory acceptance and development capabilities in place, the question then becomes one of economics. Where continuous processes enable improvements in safety or product quality they are currently being utilized on a case-by-case basis. The large investments that the pharmaceutical industry has in existing batch plants represent a significant hurdle to widespread adoption of continuous processing. Furthermore, given the high rates of attrition during development, companies may be hesitant to invest in less familiar processing technologies. Transitioning to a continuous process post-NDA also represents a significant cost and regulatory burden. While many scientists and engineers recognize the benefits of continuous processing, the transition from a batch industry to a continuous industry will likely be very slow.

23.11 SUMMARY

In this chapter, we have discussed how to implement a continuous processing paradigm for organic synthesis reactions. Converting processes from batch to continuous has the advantages of improved intermediate stability, enhanced safety, greater risk management, and enhanced mass and heat transfer. A wide range of reactors, including traditional PFRs and CSTRs, as well as novel microreactors are available for continuous processing. Knowledge of the kinetics and heats of reactions is a prerequisite for the development of a continuous process, and modeling helps to guide reactor choice and identify operating conditions. Continuous operation may not be appropriate for all processes. When looking for development opportunities, the initial focus should be on processes that have safety issues, followed by issues of quality, and lastly economics. The economic considerations are difficult to realize during process development and may not be substantial in manufacturing in the absence of integrated continuous processing. Chemical engineers can take the lead in helping the pharmaceutical industry realize all the benefits of continuous processing.

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