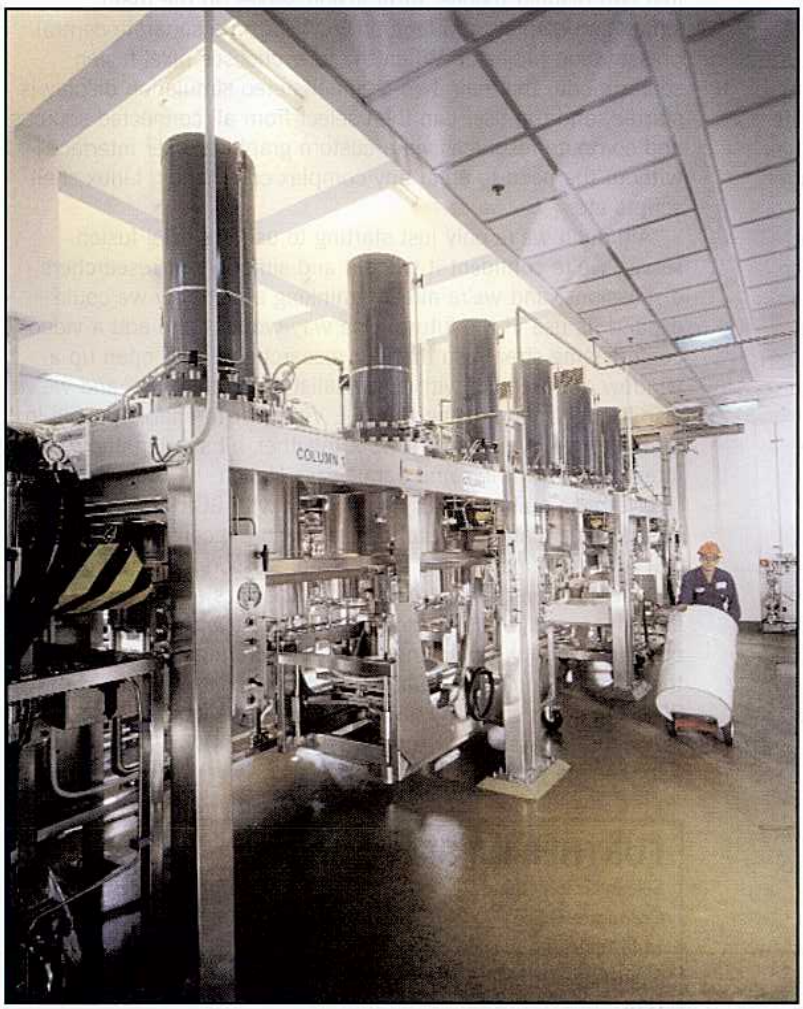
Reducing costs through continuous processing

Olivier Dapremont, Larry Zeagler and William DuBay of Ampac Fine Chemicals LLC review the development of continuous processing in the chemical industry and illustrate how the latest technologies can be applied to pharmaceutical manufacture to reduce the overall costs of API production.

With an increasing pressure to reduce drug costs, the pharmaceutical industry has been forced to find ways to reduce the manufacturing costs associated with the production of active pharmaceutical ingredients (APIs). A good example is increased outsourcing of APIs to low-cost areas of the world, where labour is inexpensive and the production costs are low. To remain competitive, Western CMOs have to achieve better performance through unique capabilities/technologies. This strategy is difficult to implement without a serious restructuring of production practices and equipment. Other industries, such as commodity chemicals, have successfully combated this problem by turning to continuous processing.



Simulated Moving Bed Chromatography is a continuous purification process approved by the FDA. The 6x800mm unit pictured is one of the six units in operation at AFC from lab to production scale.

Traditionally a batch industry

The manufacture of intermediates and active pharmaceutical ingredients (APIs) is traditionally conducted in a batch mode. Preference for a batch process is strongly based on regulatory requirements to maintain complete traceability of the product. It is easier to isolate a problem and hence minimise its economic impact when discreet batches can be quarantined. Also, batch processing is a logical scale-up of the process developed by the chemist at bench scale. In addition, batch processing provides manufacturing flexibility since in most cases it does not require specialised dedicated equipment. Unfortunately, there are many problems associated with batch processing, such as inefficient mixing, poor heat exchange, and long addition times. Also, batch processes are frequently inefficient and require large reactors, which in turn equates to a large capital investment, increased labour, and energy. This results in high production costs for material used by the pharmaceutical industry.

What kinds of processes?

In other process industries (eg commodity chemicals), a number of unit operations are conducted routinely in a continuous fashion. Distillation, for example, is conducted at very large scale to achieve high purity at low cost. Continuous concentration of a solution using wiped-film or falling-film evaporators is very common, efficient, and limits product exposure to heat. These unit operations also offer recycling capabilities that contribute to the reduction in operating cost. Liquid-liquid extraction can also be conducted continuously in equipment ranging from simple mixer/settlers to extraction columns that use a counter-current flow of liquids, combining mixing and settling sections.

Recently, continuous chromatography, or Simulated Moving Bed (SMB) technology, has been successfully transferred from the petroleum and sugar industries to the pharmaceutical industry, mainly for chiral separations.

Chemical reactions can also be conducted in a continuous fashion. There are two primary operating modes. The reactor cascade (or series of continuous stirred tanks) is the simpler one and is the combination of several batch reactors in series. One reactor feeds the next one in a continuous fashion. The residence time is

achieved by changing the number or size of reactors in the cascade. The other mode is plug flow operation, most easily achieved in the tubular reactor, where the reaction mixture is introduced at one end of a tube and the product is collected continuously at the other end. Various configurations can be found in the literature and are usually the result of a highly optimised process.

Ampac Fine Chemicals currently uses the combination of continuous chromatography and continuous evaporation (falling film) to manufacture several tonnes per year of purified API. This is a milestone in the pharmaceutical industry since this is one of the first continuous manufacturing processes for a patented API that has been approved by the FDA. The successful approval of SMB by the FDA and other regulatory authorities indicates that the time is right for greater use of continuous processing in the pharmaceutical industry.

What can continuous processing do?

The benefits of continuous processing are many. Continuous processes are typically more efficient than batch processes. The starting materials are introduced continuously into the reactor where they react on contact, and the product is continuously removed from the reaction. As a result, the concentrations of materials in the reactor are always maintained at optimum levels, limiting the chances of side reactions.

The volume of the reactor is set by the flow rate of materials and the residence time required to achieve the desired conversion. It is not dictated by the vessel size needed to contain a full batch, and is, therefore, much smaller than its batch counterpart. This has a direct effect on the heat transfer and mixing problems associated with many reactions. The process temperature can be more precisely controlled since there is a smaller quantity of reaction mixture to heat or cool. As a result, the heat of reaction can be controlled making energetic reactions safer to practice.

Over the past 50 years, AFC has used continuous processing for the synthesis of highly energetic compounds (see Box). For example, bromonitromethane is an energetic material with an explosive potential like that of trinitrotoluene (TNT). This material was successfully and safely produced at AFC in 1997 by employing a cascade of 100-gallon reactors; the capacity of this unit is 500 tonnes/year. AFC also manufactures starting materials and intermediates in a 750-gallon reactor using diazomethane generated in a continuous fashion. Diazomethane is consumed as it is formed, and at any moment in time there is only a small amount of diazomethane present in the reactor, minimising the risk involved with this highly toxic and explosive compound. Another example at AFC was the production of N-3-pentyl-dinitroxylidine (aka PROWL) in 1977 using two reactors of 100 gallon capacity in cascade format. This simple set-up had a production capacity of 2,000 tonnes/year. This reduces considerably the footprint of the process unit and consequently reduces dramatically the capital investment required.

Because there is less chance for side reactions, the product is usually of better quality, reducing the amount of work-up required to isolate the final product. This has a positive effect on the yield of the process, which impacts the required amount of starting material as well as solvent usage and waste generated. And it can result in fewer unit operations being required downstream of the reactors.

Finally, the production manpower requirement is significantly reduced since most of the operations involved can be fully controlled by automation systems. However, a very-well-trained team of chemists, engineers and operators is required to ensure proper operations during transition phases such as start-up and shut-down of the process.

Paradigm shift

The pharmaceutical industry is under pressure to reduce cost while maintaining quality and safety. Continuous processing is safer, more efficient, requires less reactor volume for higher throughput with better product purity, and can be conducted with a smaller crew of well-trained operators and technicians. All these factors tend to reduce significantly the cost of production. In the next few years a major paradigm shift in the fine chemical industry will occur in favour of continuous processing. AFC's goal is to help pharma customers reduce their cost of goods, without sacrificing quality or safety, by leveraging over 50 years of experience in developing continuous processes. sp²

CONTINUOUS PROCESSING: AN HISTORICAL PERSPECTIVE

Hydroxylethylethylenimine (HEEI)
A production capacity of 1,250 tonnes per annum was achieved in 1974 with a cascade of three 90-gallon reactors. The product was recovered via flash evaporation while the solvent was recycled by fractional distillation.

N-3-pentyl-di-nitroxylidine (PROWL)
Two 100-gallon reactors in cascade combined with a continuous-phase extraction allowed Aerojet Fine Chemicals (AFC's former name) to produce PROWL with a capacity of 2,000 tonnes per annum in 1977.

Ethylene imine (EI)
The production of ethylene imine, a highly volatile and toxic compound, was conducted in 1979 at the rate of 2,000 tonnes per year with the combination of cascading reactors and fractional distillation.

Bromonitromethane (BMN)
More recently, in 1997, a capacity of 500 tonnes per annum was achieved with 100-gallon reactors combined with fractional distillation.

Diazomethane
Diazomethane is a very reactive toxic and explosive gas that is useful for a variety of transformations. AFC was a pioneer in the safe application of diazomethane at commercial scale using remotely-controlled processing bays. Continuous generation/consumption of diazomethane vapour/liquid has allowed AFC to safely produce over 1,200 batches of cGMP products using diazomethane at 750-gallon scale.

FURTHER INFORMATION

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