Chiral Separations

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In mid-1992, a simple four-page document published by the U.S. Food and Drug Administration (FDA) created broad and deep ripples throughout the world's drug development community. In that document, the FDA's Center for Drug Evaluation and Research (CDER) enumerated, for the first time, the proper development guidelines for *stereoisomeric* drugs. The CDER guidance concluded that, although drug substances had previously been successfully and safely developed and implemented as racemic mixtures, there have been several high-profile cases in which the *enantiomers* were found to have different pharmacologic and toxicologic impact, producing therapeutic problems (Anon, 1992). Perhaps, the most well-documented example is that of the drug substance thalidomide. First marketed by a German pharmaceutical company in 1956 for respiratory infections, it was later prescribed in concert with other chemicals as a sedative and for treatment of morning sickness. While the S-enantiomer was later proven to indeed produce therapeutic effects, the R-enantiomer was confirmed to be a teratogen and was subsequently linked to physical birth defects (Hoffman, 1997).

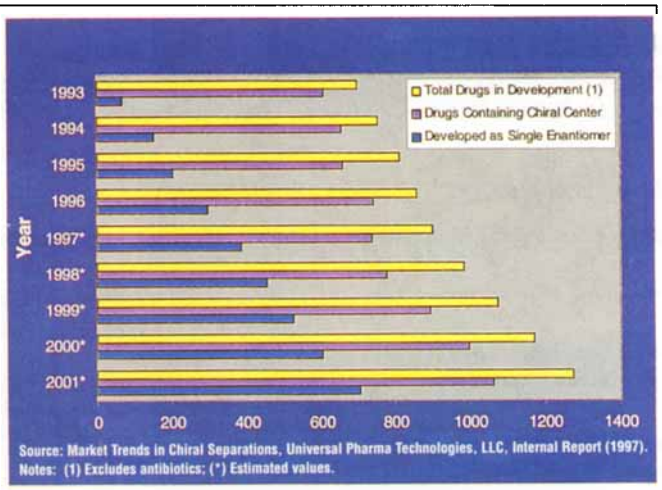

Figure 1. Distribution of drugs in development worldwide.

It can be argued that the long-term effects of R-thalidomide would not have surfaced even under the current FDA guidelines for drug acceptance, particularly because of the unusual interconversion between R- and S-thalidomide which occurs in biological systems. However, the current FDA policy provides a new and necessary level of assurance against the recurrence of such tragedies. The FDA policy requires drug developers to: (a) quantitate the pharmacological and toxicological effects of each enantiomer, and (b) produce a single enantiomer drug substance if the results of either the pharmacokinetics or the toxicology of the enantiomers is significantly different so as to affect drug dosing or side-effects. The FDA now requires these evaluations to be performed and described in detail in Investigational New Drug (IND) and New Drug Application (NDA) submissions.

Prior to 1990, the question of chiral purity in drug substances was an academic issue. Such information was of potential interest for understanding and classifying the biotransformation of the drug substance, but of little importance for product launch since the methods for production of single enantiomers were limited in applicability. The FDA's guidelines had two immediate effects. The first was to shift the drug development landscape toward the implementation of single enantiomers, as illustrated in Figure 1. The second effect was to stimulate the development of novel techniques for *asymmetric* synthesis and enantiomeric separations. As often occurs in the chemical industry, governmental regulation produced a technological need and, essentially, created new research and development opportunities for inventive engineers and scientists. Cost- and time-efficient techniques were immediately required which could provide the quantities of material necessary for toxicology testing and, potentially, commercial production. Between 1992 and 2000, the world market for optically pure chemical compounds increased from $30 billion to an estimated $100 billion (Anon, 1997), with nearly two dozen companies now specializing in chiral separations.

Since that time, the growth of a single enantiomer drug substances has been matched by the growth of asymmetric methods, both in synthesis and separation, which can provide the required materials. While asymmetric synthesis techniques have improved to allow a variety of compounds to be directly synthesized with high chiral purity, yields of these processes are often low or moderate at best. Conversely, chiral separation techniques can provide near quantitative yields of each enantiomer, however, they are perceived as expensive and inefficient if the undesired enantiomer cannot be utilized in some manner. The goal of this article is to briefly overview *chiral* separation techniques, both those currently in commercial practice as well as emerging technologies. Efficiencies are highlighted, in both time and material resources, which can be exploited by separation techniques. The closing remarks focus on the role of chemical engineers must play in the drug development industry and the successful adoption of these techniques.

Chiral separation methodologies

A wide variety of techniques for chiral separations have been developed in the past 15 years. Some techniques mimic the manner in which biological systems distinguish chirality; others exploit

minor differences in physical properties or interactions with other chemical entities.

Crystallization

Some chiral compounds can be obtained directly through crystallization of the desired enantiomer from the racemic mixture. Normally, enantioselective crystallization occurs following the seeding of a supersaturated solution of the racemic mixture with a crystal of desired enantiomer. In a few cases, enantioselective nucleation and crystal growth can occur without seeding under the appropriate conditions. It has been estimated that enantioselective crystallization accounts for roughly one-fifth of the chiral separations performed at scales equal or exceeding 1 kg of product (Anon, 1997). The popularity of crystallization is a direct result of the ease of operation and the cost of manufacture. When this technique is possible and efficient, it is the chiral separation method of choice. However, often fractional crystallization trains must be employed (Schweitzer, 1988) in order to provide sufficient material recoveries, adding to processing times and expense.

Figure 2. Largest cGMP validated Simulated Moving Bed unit operating in North America for chiral separations in the pharmaceutical industry.
Located at Universal Pharma Technologies, LLC, North Andover, MA.

Kinetic resolutions

Resolutions based on kinetic effects in chemical reactions can be one of several major types, but are typically divided between enzyme and inorganic catalyzed systems. Both major systems operate in much the same manner. In general, a material capable of enantiomeric differentiation is used to catalyze a chemical transformation of the two enantiomers at substantially different rates. Typically, either enantiomer can be resolved by the proper selection of the enantiomerically differentiating material (Faber, 1997). While powerful, effective, and capable of producing very high enantiomeric excess in some situations, application is limited due to lengthy development times and availability of enantiomerically differentiating materials.

Reaction/resolution combinations

Resolution of individual enantiomers from mixtures via serial combinations of reaction and resolution techniques are an often-practiced route to chiral purity. Examples include reaction to form a diastereomeric salt coupled with classical resolutions. While not chiral separation techniques *per se,* they are included here for their importance in obtaining enantiomerically pure materials. A relatively new technique emerging in the past 10 years has been the use of enzymes to selectively catalyze the reaction of one enantiomer into a different chemical species (Faber, 1997). An example of this is the use of pig liver esterase to catalyze the esterification of an undesired enantiomer, followed by the application of standard physical separation techniques (e.g., crystallization, evaporation, etc.). Diastereomeric salt resolutions are widely applied in enantiospecific chemistry and are generally accepted as the most cost effective method, where applicable. However, racemization of the separated enantiomers can often occur during the elimination of the salt, rendering this technique useless. Enzymatic methods, though growing in importance, are limited by the inability of most enzymes to survive typical organic solvents used in pharmaceutical processing. In addition, enzyme cost and development time can hamper the application of the technique.

Membrane-based separations

Early work with supported liquid membranes showed great promise for the selective transport of specific enantiomeric forms across membranes. However, commercial application has been very limited due to the extremely poor stability of supported liquid membranes. Significant research activity has been recently focused on improving the stability of the supported liquid membranes with some success. If the stability of liquid membranes can be sufficiently improved, this emerging technique offers the opportunity to significantly alter the panorama of chiral separations. Properly developed, liquid membrane separations would likely provide the lowest capital, lowest operating cost process to achieve chiral purity through separation.

Liquid chromatography

One of the first techniques to gain widespread practical acceptance, preparative high-pressure liquid chromatography (HPLC) has been used for production of relatively small quantities of chiral substances since stationary phases possessing enantiomeric recognition were invented. In preparative HPLC, the proper combination of stationary phase and mobile phase is chosen which

allows the enantiomeric mixture to be eluted from a column of the stationary phase at distinct times. In performing repetitive injections of the enantiomeric mixture and collecting the effluent from the column in appropriate time segments, separation into the pure enantiomers can be performed. This technique, however, employs a substantial amount of solvent and requires significant capital investment in the form of expensive stationary phase and high-pressure equipment. In addition, the product stream is obtained from the process in extremely dilute form, resulting in significant energy expenditure to recover the desired compound.

Several novel adaptations of preparative HPLC have been invented to attempt to overcome these issues. Perhaps, the most important of these techniques is the adaptation of the so-called Simulated Moving Bed (SMB) Countercurrent Adsorptive Separation process invented by UOP in the late 1950s to the chiral separations field. This separation method overcomes many of the limitations of preparative HPLC described above through increases in solvent efficiency, solvent management, adsorbate concentration, and stationary phase utilization. Though heavily applied in the petrochemical industry, it has only recently been effectively applied in the separation of pharmaceutical compounds on the moderate and large scale. Figure 2 shows an example of a current Good Manufacturing Practices (cGMP) validated SMB unit in use for pharmaceutical chiral separations in North America.

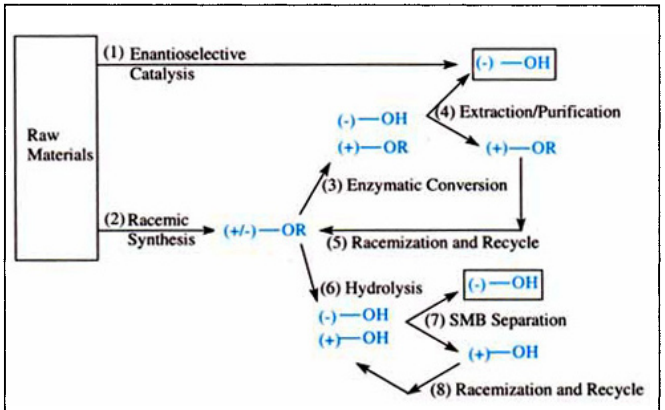

Figure 3. Three routes to chiral alcohol synthesis.

Chiral separations vs. asymmetric synthesis: an example

The design of separation processes can have a tremendous impact on the pharmaceutical industry. The following example makes this point clear. This example, while compiled from numerous individual projects—some experimental and some investigations on paper—performed within the authors' organization over the past year, is representative of the difficult process economic questions which must be addressed.

Consider a key chiral pharmaceutical intermediate which is required to be produced in high enantiomeric excess; the chiral center formed in this intermediate is retained through the remainder of the process steps. Two general options exist for chemical process development for the key intermediate: an enantiospecific synthesis can be developed, or a route to form the racemic mixture can be developed in combination with a chiral separation.

Two different chiral separation methods are selected: (A) a reactive/separation technique, and (B) separation using simulated moving bed chromatography. Three metrics of "project success" were calculated for the two resolution methods: time-to process in man-months, cost-to-process, and cost of production. The metrics for the two separation technologies were then compared against estimated metrics for a proposed enantioselective synthesis route for the intermediate. The goal of this procedure was to provide an "economic benchmark" from the separation process development to determine if the time and expense of developing an enantiospecific synthesis was justified. Figure 3 summarizes the three different routes to chiral purity.

The cost metrics resulting from this investigation, summarized in Table 1, provide a convincing argument for combining traditional, racemic chemical synthesis with chiral separations for attaining high enantiomeric excess. Indeed, the time- and cost-to-process metrics show substantial savings relative for chiral separation routes compared to enantioselective synthesis. This is primarily due to the ease with which chiral separation processes, particularly liquid chromatography processes such as simulated moving bed, can be developed and scaled to commercial practice. In general, the modeling capabilities and engineering scale-up challenges are significantly reduced for separation techniques compared to enantio-selective synthesis. These cost- and time-to-process advantages cannot be overstated. While the overall advantage of time-to-market in the pharmaceutical industry can be difficult to measure, it has been estimated that a competitive product arriving to market six months after the initial product is likely to achieve no more than one-half the revenues of the initial product (Cooper, 1993). In addition, delay in launch of a blockbuster pharmaceutical product by only *one month* can cause a delay or loss of revenues of at least $5 million and perhaps as much as $50 million over the life of the product (Cooper, 1993).

Perhaps, surprisingly, the cost of manufacture obtained through the combination of chiral separations and racemic chemical synthesis can be cost-competitive with an enantioselective synthesis depending on the ultimate fate of the unwanted enantiomer. If the undesired enantiomer can be easily converted back into the racemic mixture (Steps 5 and 8, Figure 3), production through chiral separation is generally the low-cost route to chiral purity since raw material efficiency is greatly increased. If, however, such a racemization is not possible, the cost of raw materials becomes a significant influence on the economic acceptance of a chiral separation route since at least one-half of the raw materials will not end up in the desired product. In such cases, enantioselective synthesis may provide superior cost of manufacture depending on the overall yield of the synthesis.

Future challenges

The previous example illustrates the potential importance chiral separation techniques can have on time-to-market and overall process economics. It is therefore quite surprising how few products in the pharmaceutical industry currently take advantage of these potential advantages. Indeed, the application of chiral separations in pharmaceutical manufacturing processes has been described as a "failure" or a last resort: something to apply only if enantioselective synthesis is impossible. This view is shortsighted. Chemical engineers have been familiar with and actively applying the concept of combining indi-

vidual unit operations of reaction, separation, and recycle for improved process economics for more than 80 years. One can only speculate as to the reasons behind the dearth of examples. One potential explanation is the historically minor role of chemical engineers in pharmaceutical process development. While this has changed rapidly in the past 15 years with the hiring of large numbers of chemical engineers into the industry, the majority of process development in pharmaceuticals is still directed and carried out by chemists.

While the role of the chemist is essential in pharmaceutical process development, so too is the role of the chemical engineer. As competition, and potentially government regulation, begin to threaten the comfortable margins pharmaceutical companies have enjoyed on dominant products, it will become even more essential to design entire processes for drug manufacture which have been integrated for maximum cost efficiency. In many cases, enantioselective synthesis will remain the most elegant and most cost-effective route of pharmaceutical production. In many others, chiral separations combined with traditional, racemic synthesis reactions will provide an alternative, low-cost solution, elegant in a synchronous relationship with the overall production process. As in other industries, it will become increasingly the responsibility of the practicing chemical engineer to provide the intuition and leadership required to cham-pion the application of processes, techniques, and methods which improve pharmaceutical process economics. Integrating chiral separations into the process development lexicon of the pharmaceutical industry should be a principal method to improve process economics.

Table 1: Process Cost Metrics for Production of a Chiral Alcohol.

	Time-to-Process (man-months)	Cost-to-Process U.S. $(000's)	Cost of Production $/kg
Enantioselective Synthesis	22	$711.0	$325
Reaction/Separation Sequence			
w/o Racemization	7	$237.0	$570
w/ Racemization	8	$257.0	$330
Simulated Moving Bed Separation			
w/o Racemization	5	$169.0	$580
w/ Racemization	6	$200.0	$320

Note: A production volume of 5 metric tons per annum was assumed.

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