ADSORPTION, LIQUID SEPARATION

1. Introduction

Recovery and purification of the desired product are generally as important as the synthesis of the product itself. Although most of the value in chemical conversion is added via reaction, it is the separation that largely determines the capital cost of production. Nearly every chemical manufacturing operation requires the use of separation processes to recover and purify the desired product. In most circumstances, the efficiency of the separation process has a significant impact on both the quality and the cost of the product (1). Liquid-phase adsorption has long been used for the removal of contaminants present at low concentrations in process streams. In most cases, the objective is to remove a specific feed component; alternatively, the contaminants are not well defined, and the objective is to improve feed quality as defined by color, taste, odor, and storage stability (2). Deodorization of water, decolorization of sugar, ion exchange of fermentation broths are a few examples of processes in which trace impurities are removed. More recently the simulated moving bed (SMB) processes are finding applications in Biotechnology semi batch and in protein purification.

While most of the strategies to remove trace impurities are batch processes, bulk adsorptive separation processes are continuous or semicontinuous in operation, because in bulk separation processes, where the feed component may be present in large enough concentration, it is imperative to maximize utilization of the adsorbent. The Hypersorption process (3) developed by Union Oil Company in the early 1950s for the recovery of propane and heavier components from natural gas is the earliest example of large-scale countercurrent adsorption processes.

The first commercial operation of a liquid-phase simulated countercurrent adsorption process occurred in 1960 with the advent of the Molex process discovered by Universal Oil Products (UOP), for recovery of high purity *n*-paraffins (4–6). Since that time, bulk adsorptive separation of liquids has been used to solve a broad range of problems, including individual isomer separations and class separations. The commercial availability of synthetic molecular sieves and ion-exchange resins and the development of novel process concepts have been the two significant factors in the success of these processes.

This article is devoted mainly to the theory and practice of batch and continuous liquid-phase bulk adsorptive separation processes.

2. Batch versus Continuous Operation

Industrial-scale adsorption processes can be classified as batch or continuous (7,8). In a batch process, the adsorbent bed is saturated and regenerated in cyclic operation. In a continuous process, a countercurrent staged contact between the adsorbent and the feed and desorbent is established by either a true or a simulated recirculation of the adsorbent. The efficiency of an adsorption process is

significantly higher in a continuous mode of operation than in a cyclic batch mode (9). In a batch chromatographic operation, the liquid composition at a given level in the bed undergoes a cyclic change with time, and large portions of the bed do not perform any useful function at a given time. In continuous operation, the composition at a given level is invariant with time, and every part of the bed performs a useful function at all times. The height equivalent of a theoretical plate (HETP) in a batch operation is roughly three times that in a continuous mode. For difficult separations, batch operation may require 25 times more adsorbent inventory and twice the desorbent circulation rate than does a continuous operation. In addition, in a batch mode, the four functions of adsorption, purification, desorption, and displacement of the desorbent from the adsorbent are inflexibly linked, whereas a continuous mode allows more degrees of freedom with respect to these functions, and thus a better overall operation.

3. Continuous Countercurrent Processes

The need for a continuous countercurrent process arises because the selectivity of available adsorbents in a number of commercially important separations is not high. In the *p*-xylene system, eg, if the liquid around the adsorbent particles contains 1% *p*-xylene, the liquid in the pores contains ~2% *p*-xylene at equilibrium. Therefore, one stage of contacting cannot provide a good separation, and multistage contacting must be provided in the same way that multiple trays are required in fractionating materials with relatively low volatilities. A number of commercial moving-bed designs exist mainly for ion exchange. A good review of these designs can be found in (10).

The multistage countercurrent contacting concept was originally used in a process developed and licensed by UOP under the name Sorbex (11,12). Other versions of the SMB system are also used commercially for industrial scale separations (13). Toray Industries built the Aromax process for the production of *p*-xylene (14–16). Illinois Water Treatment and Mitsubishi have commercialized SMB processes for the separation of fructose from dextrose (17–19). Institut Francais du Petrole have commercialized the Eluxyl process for production of *p*-xylene (21). More recently, SMB processes are finding increased application in the purification of specialty chemicals, enantiomers, vitamins and proteins (22,23). Particularly in the area of drug development, the advent of SMB has provided a high throughput, high yield, solvent efficient, safe and cost effective process option.

The following discussion involves the principles and practice of the SMB processes for liquid-phase separation.

4. Moving-Bed Operation

A hypothetical moving-bed system and a liquid-phase composition profile are shown in Figure 1. The adsorbent circulates continuously as a dense bed in a closed cycle and moves up the adsorbent chamber from bottom to top. Liquid

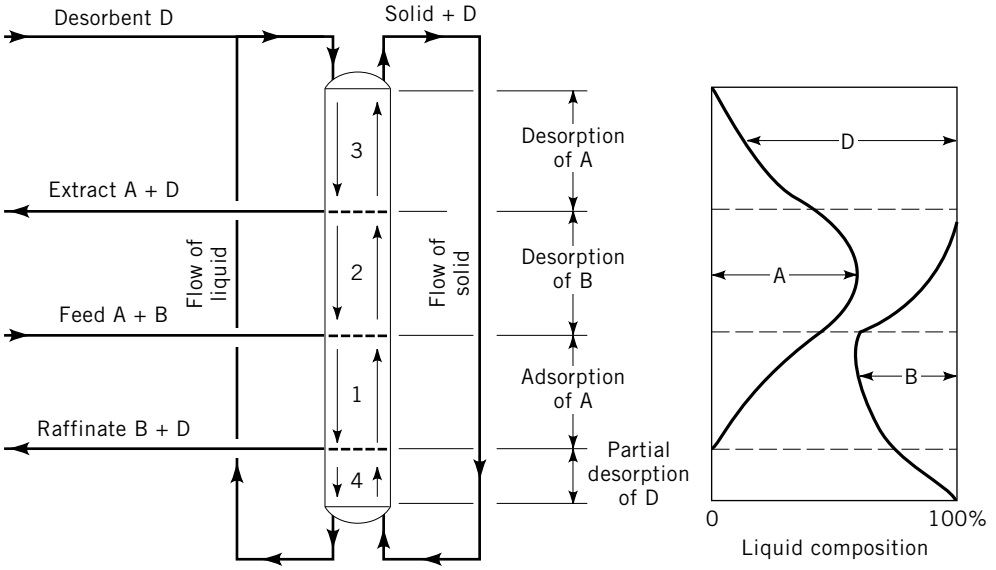

Fig. 1. Adsorptive separation with moving bed.

streams flow down through the bed countercurrently to the solid. The feed is assumed to be a binary mixture of A and B, with component A being adsorbed selectively. Feed is introduced to the bed as shown.

Desorbent D is introduced to the bed at a higher level. This desorbent is a liquid of different boiling point from the feed components and can displace feed components from the pores. Conversely, feed components can displace desorbent from the pores with proper adjustment of relative flow rates of solid and liquid.

Raffinate product, consisting of the less strongly adsorbed component B mixed with desorbent, is withdrawn from a position below the feed entry. Only a portion of the liquid flowing in the bed is withdrawn at this point; the remainder continues to flow into the next section of the bed. Extract product, consisting of the more strongly adsorbed component A mixed with desorbent, is withdrawn from the bed; again, only a portion of the flowing liquid in the bed is withdrawn, and the remainder continues to flow into the next bed section.

The positions of introduction and withdrawal of net streams divide the bed into four zones, each of which performs a different function as described below.

Zone 1. The primary function of this zone is to adsorb A from the liquid.

Zone 2. The primary function of this zone is to remove B from the pores of the solid.

Zone 3. The function of this zone is to desorb A from the pores.

Zone 4. The purpose of this zone is to act as a buffer to prevent component B, which is at the bottom of *Zone 1*, from passing into *Zone 3*, where it would contaminate extracted component A.

4.1. Difficulties of Moving-Bed Operation. The use of a moving bed introduces the problem of mechanical erosion of the adsorbent. Obtaining uniform flow of both solid and liquid in beds of large diameter is also difficult. The performance of this type of operation can be greatly impaired by nonuniform flow of either phase.

The use of a series of fluidized beds may be considered when solid overflows from each bed to the next. However, this arrangement involves a sacrifice in mass-transfer efficiency because the number of theoretical equilibrium trays cannot exceed the number of physical beds. In contrast, the flow through dense and fixed beds of adsorbent, as practiced in chromatography, can provide hundreds of theoretical trays in beds of modest length. In view of these difficulties, only a few fluidized-bed operations are practiced commercially. The Purasiv HR system, developed by Union Carbide Corporation, used beaded activated carbon for the recovery of solvent. This process used a staged fluidized bed for adsorption and a moving bed for regeneration (24).

4.2. Simulated Moving Bed Operation. In the moving-bed system of Figure 1, solid is moving continuously in a closed circuit past fixed points of introduction and withdrawal of liquid. The same results can be obtained by holding the bed stationary and periodically moving the positions at which the various streams enter and leave. A shift in the positions of the introduction of the liquid feed and the withdrawal in the direction of fluid flow through the bed simulates the movement of solid in the opposite direction.

Of course, moving the liquid feed and withdrawal positions continuously is impractical. However, approximately the same effect can be produced by providing multiple liquid-access lines to the bed and periodically switching each stream to the adjacent line. Functionally, the adsorbent bed has no top or bottom and is equivalent to a toroidal bed. Therefore, the four liquid-access positions can be moved around the bed continually, always maintaining the same distance between the various streams.

The commercial application of this concept (25) is portrayed in Figure 2, which shows the adsorbent as a stationary bed. A liquid circulating pump is provided to pump liquid from the bottom outlet to the top inlet of the adsorbent chamber. A fluid-directing device known as a rotary valve (26,27) is provided. The rotary valve functions on the same principle as a multiport stopcock in directing each of several streams to different lines. At the right-hand face of the valve, the four streams to and from the process are continuously fed and withdrawn. At the left-hand face of the valve, a number of lines are connected that terminate in distributors within the adsorbent bed. The rotary valve is the most widely used method in industrial scale applications for accomplishing the stepwise movement of external streams from bed to bed. This same function can be accomplished using manifolds of on–off valves (28,29). For a 24-bed process application, >100 such valves could be required. Small scale SMB applications, such as for chiral separations, make extensive use of switching valves (2,29).

At any particular moment, only four lines from the rotary valve to the adsorbent chamber are active. Figure 2 shows the flows at a time when lines 2, 5, 9, and 12 are active. When the rotating element of the rotary valve is moved to its next position, each net flow is transferred to the adjacent line;

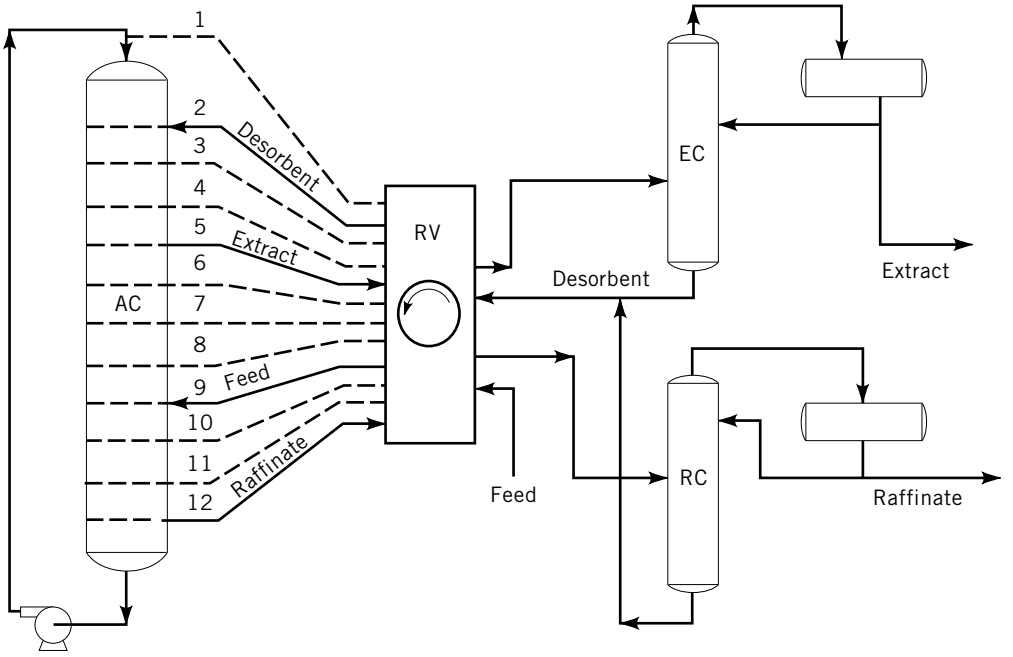

Fig. 2. Simulated moving-bed process for adsorptive separation. AC = adsorbent chamber, RV = rotary valve, EC = extract column, RC = raffinate column.

thus, desorbent enters line 3 instead of line 2, extract is drawn from 6 instead of 5, feed enters 10 instead of 9, and raffinate is drawn from 1 instead of 12.

Figure 1 shows that in the moving-bed operation, the liquid flow rate in each of the four zones is different because of the addition or withdrawal of the various streams. In the simulated moving-bed of Figure 2, the liquid flow rate is controlled by the circulating pump. At the position shown in Figure 2, the pump is between the raffinate and desorbent ports, and therefore should be pumping at a rate appropriate for *Zone 4*. However, after the next switch in position of the rotary valve, the pump is between the feed and raffinate ports, and should therefore be pumping at a rate appropriate for *Zone 1*. Stated briefly, the circulating pump must be programmed to pump at four different rates. The control point is altered each time an external stream is transferred from line 12 to line 1.

To complete the simulation, the liquid-flow rate relative to the solid must be the same in both the moving-bed and simulated moving-bed operations. Because the solid is physically stationary in the simulated moving-bed operation, the liquid velocity relative to the vessel wall must be higher than in an actual moving bed operation.

The primary control variable at a fixed feed rate, as in the operation pictured in Figure 2, is the cycle time, which is measured by the time required for one complete rotation of the rotary valve (this rotation is the analogue of adsorbent circulation rate in an actual moving-bed system), and the liquid flow rate in *Zones 2–4*. When these control variables are specified, all other net rates

to and from the bed and the sequence of rates required at the liquid circulating pump are fixed. An analysis of sequential samples taken at the liquid circulating pump can trace the composition profile in the entire bed. This profile provides a guide to any changes in flow rates required to maintain proper performance before any significant effect on composition of the products has appeared. Various aspects of process control are described in the patent literature (30–38).

Temperature and pressure are generally not considered as primary operating variables: Temperature is set sufficiently high to achieve rapid mass-transfer rates, and pressure is sufficiently high to avoid vaporization. In liquid-phase operation, as contrasted to vapor-phase operation, the required bed temperature bears no relation to the boiling range of the feed, an advantage when heat-sensitive stocks are being treated.

4.3. Theoretical Modeling of SMB Systems. The McCabe–Thiele approach has been adapted to describe the SMB process (39). Two feed components, A and B, with a suitable adsorbent and a desorbent, C, are separated in an isothermal continuous countercurrent operation. If A is the more strongly adsorbed component and the system is linear and non-interacting, the flows in each section of the process must satisfy the following constraints for complete separation of A from B:

Section	*Condition*
IV	$SI(D + F - E - R) > K_{CB}$
I	$SI(D + F - E) > K_{BA}$
II	$SI(D - E) < K_{AB}$
III	$S/D < K_{CA}$

The required direction of the net flow of each component is illustrated in Figure 3. The SMB process has four flow-rate variables *(SIF, DIF, EIF*, and *RIF)* and four inequality constraints, one for each section of the bed. Once the equilibrium is fixed, the only remaining degree of freedom is the margin by which the inequality constraints are fulfilled. Once that is decided, the inequality constraints become four equations that define all flow-rate ratios for the system. Once the flow rates are fixed, a preliminary estimate of the number of theoretical stages in each section may be obtained by a McCabe–Thiele diagram, shown in Figure 4.

McCabe–Thiele diagrams for nonlinear and more practical systems with pertinent inequality constraints are illustrated in Figures 5 and 6. The convex isotherms are generally observed for zeolitic adsorbents, particularly in hydrocarbon separation systems, whereas the concave isotherms are observed for ion exchange resins used in sugar separations. Many types of adsorbents have been used in large scale SMB processes. These include amorphous inorganic materials such as silica, alumina; crystalline inorganic materials such as zeolites; organic materials such as activated carbon and polymeric materials such as strong acid, base resins. More recently, specialized adsorbents for chiral–enantiomer separations have been used in an SMB mode. The adsorbent plays a major role in determining the effectiveness of the separation processes. Selectivity, capacity and

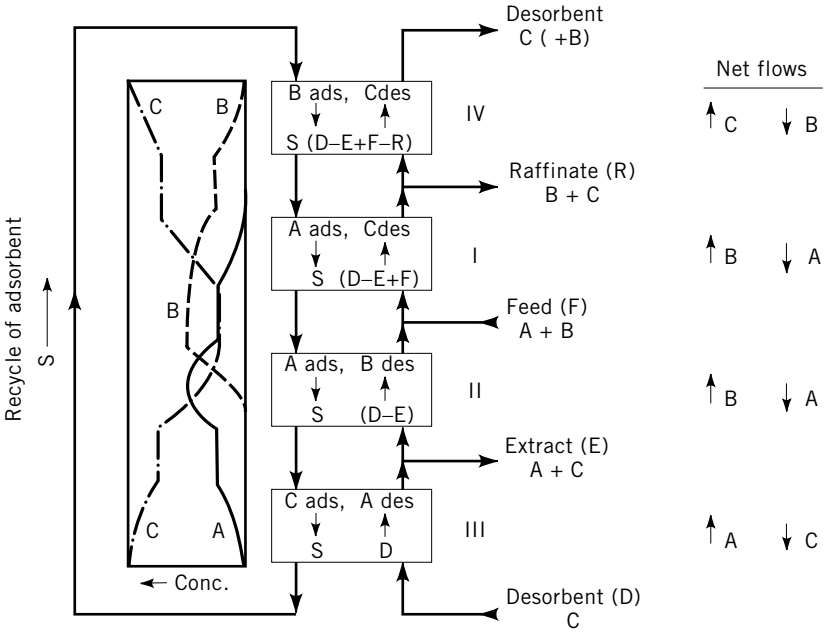

Fig. 3. Schematic diagram of the SMB process *D, E, F, R*, and *S* represent flow rates for desorbent, extract, feed, raffinate, and net solids, respectively.

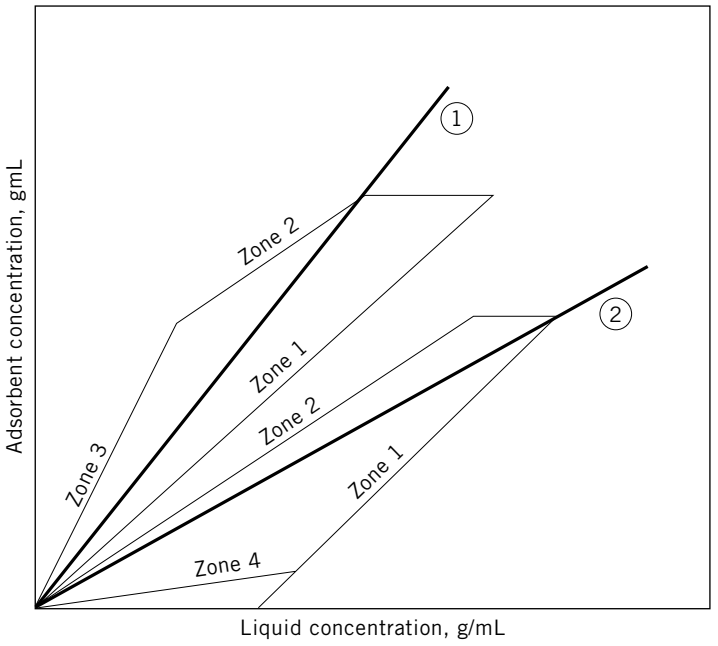

Fig. 4. SMB operation with linear isotherms. Slope of *(D KI;* slope of *M K2*. Conditions for separation: *K*, < *K2, L31S*∼!! *K1K2 !*∼ *L2IS:!*,∼*K1, K2:!*LIIS:!∼*K1, L4*/*S :!*∼−*K2, L,* −*L2* = *F*; where *K* = adsorption coefficient, *L* = net liquid flow rate, *S* net solids flow rate, and *F* = feed flow rate.

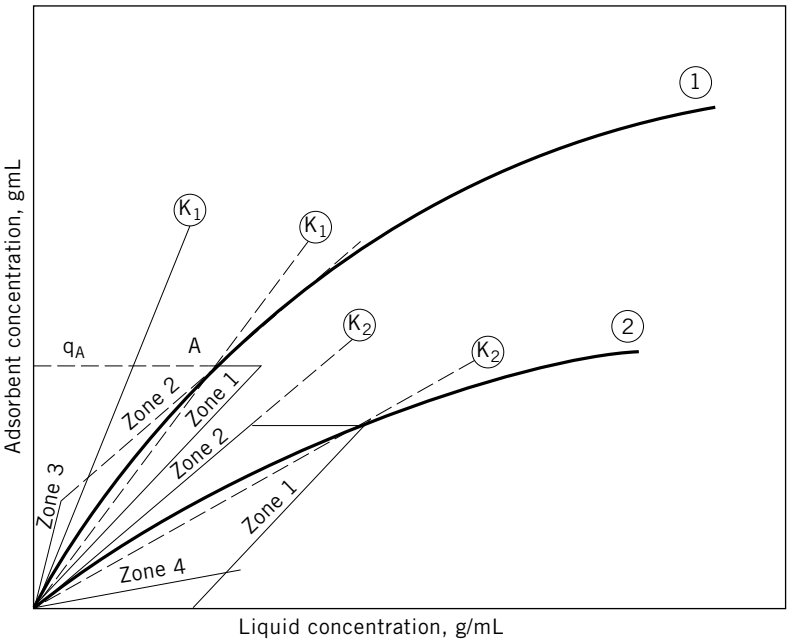

Fig. 5. SMB operation with convex isotherms. Conditions for separation: at point A, slope of (*D K2, K, >K2, L31S* ∼t *K1*, *K2:!*∼ *L21S : 5KT:!*∼*K1*, *K*∼:!∼ *LIIS*K1, *L4IS K*∼, *L, −L2 F*, where *K, L, S*, and *F* are as defined in Figure 4.

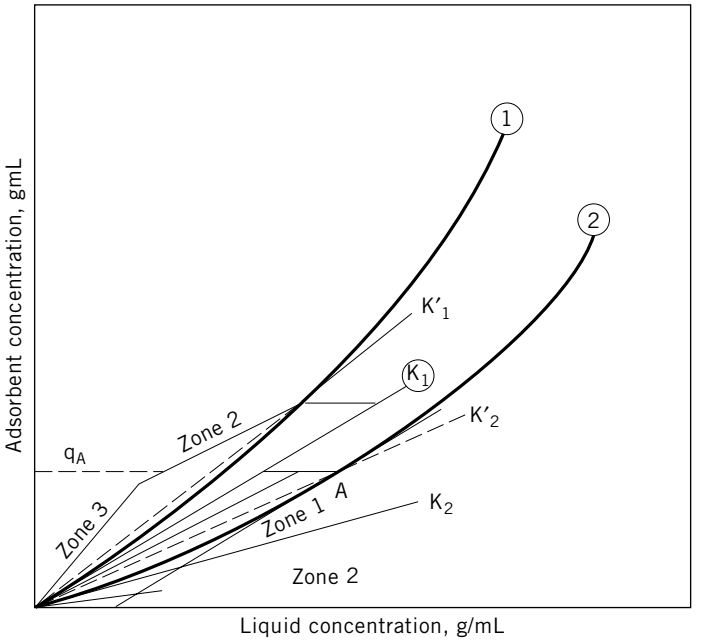

Fig. 6. Conditions for separation: At point A, slope of *K1, K, >K2, L31S >K'*j, *K2 :5KT* ∼ *9 L11S* :!∼*KI*, *K*∼ : *5 L21S :! Kj, L41S :!*∼ *K2*; where *K, L*, and *S* are as defined in Figure 4. Adsorbent concentration of component 2 < q*A*.

mass transfer rate are determined largely by the adsorbate–adsorbent interactions.

5. Adsorbate–Adsorbent Interactions

An adsorbent can be visualized as a porous solid having certain characteristics. When the solid is immersed in a liquid mixture, the pores fill with liquid, which at equilibrium differs in composition from that of the liquid surrounding the particles of the adsorbent. These compositions can then be related to each other by enrichment factors that are analogous to relative volatility in distillation. The adsorbent is selective for the component that is more concentrated in the pores than in the surrounding liquid.

The choice of separation method to be applied to a particular system depends largely on the phase relations that can be developed by using various separative agents. Adsorption is usually considered to be a more complex operation than is the use of selective solvents in liquid–liquid extraction (see EXTRACTION, LIQUID–LIQUID), extractive distillation, or azeotropic distillation (see DISTILLATION, AZEOTROPIC AND EXTRACTIVE). Consequently, adsorption is employed when it achieves higher selectivities than those obtained with solvents.

An example of unique selectivities is the separation of olefins from paraffins in feed mixtures containing about five successive molecular sizes, eg, C_{10} to C_{14}. Liquid–liquid extraction might be considered for this separation. However, polar solvents give solubility patterns of the type shown in Figure 7. Each olefin is more soluble than the paraffin of the same chain length, but the solubility of both species declines as chain length increases.

Thus in a broad boiling mixture, solubilities of paraffins and olefins overlap and separation becomes impossible. In contrast, the relative adsorption of olefins and paraffins from the liquid phase on the adsorbent used commercially for this operation is shown in Figure 8. Not only is there selectivity between an olefin and paraffin of the same chain length, but also chain length has little effect on

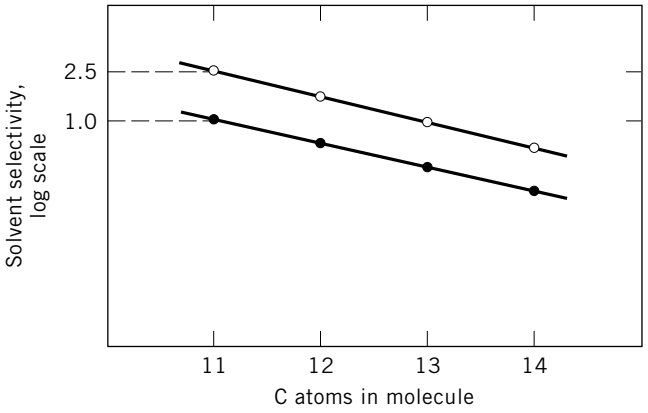

Fig. 7. Liquid–liquid extraction selectivity: olefins; paraffins.

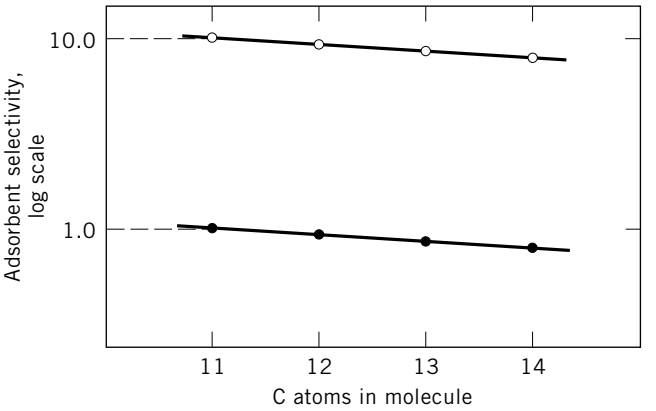

Fig. 8. Liquid-phase selectivity of UOPs Olex adsorbent; olefins; paraffins.

selectivity. Consequently, the complete separation of olefins from paraffins becomes possible.

Unique adsorption selectivities are employed in the separation of C_8 aromatic isomers, a classical problem that cannot be easily solved by distillation, crystallization, or solvent extraction (10). Although *p*-xylene [106-42-3] can be separated by crystallization, its recovery is limited because of the formation of eutectic with *m*-xylene [108-58-3]. However, either *p*-xylene, *m*-xylene, *o*-xylene [95-47-6], or ethylbenzene [100-41-4] can be extracted selectively by suitable modification of zeolitic adsorbents.

Literature dealing with adsorbent–adsorbate interactions in liquid phase is largely confined to patents (40–81). Although theoretical consistency tests exist for such data (82), the search for an adsorbent of suitable selectivity remains an art.

Recent publication by Pharmacia (83) illustrates the adsorbate–adsorbent interactions in extremely difficult separations of chiral molecules. Here the mobile phase or the desorbent is also employed to amplify selectivites via the use of phenomenon generally known as reversed phase chromatography.

6. Practical Adsorbents

The search for a suitable adsorbent is generally the first step in the development of an adsorption process. A practical adsorbent has four primary requirements: selectivity, capacity, mass-transfer rate, and long-term stability. The requirement for adequate adsorptive capacity restricts the choice of adsorbents to microporous solids with pore diameters ranging from a few tenths to a few tens of nanometers.

Traditional adsorbents such as silica [7631-86-9], SiO_2 activated alumina [1318-23-61], A1203; and activated carbon [7440-44-0], C, exhibit large surface areas and micropore volumes. The surface chemical properties of these adsorbents make them potentially useful for separations by molecular class. However,

the micropore size distribution is fairly broad for these materials (84). This characteristic makes them unsuitable for use in separations in which steric hindrance can potentially be exploited (see ALUMINUM COMPOUNDS, ALUMINA; SILICON COMPOUNDS, SYNTHETIC INORGANIC SILICATES).

Typical polar adsorbents are silica gel and activated alumina. Equilibrium data have been published on many systems (40–47,85,86). The order of affinity for various chemical species is saturated hydrocarbons < aromatic hydrocarbons = halogenated hydrocarbons < ethers = esters = ketones < amines = alcohols ≤ carboxylic acids. In general, the selectivities are parallel to those obtained by the use of selective polar solvents; in hydrocarbon systems, even the magnitudes are similar. Consequently, the commercial use of these adsorbents must compete with solvent-extraction techniques.

The principal nonpolar-type adsorbent is activated carbon. Equilibrium data have been reported on hydrocarbon systems, various organic compounds in water, and mixtures of organic compounds (40,41,45,85,86). With some exceptions, the least polar component of a mixture is selectively adsorbed; eg, paraffins are adsorbed selectively relative to olefins of the same carbon number, but dicyclic aromatics are adsorbed selectively relative to monocyclic aromatics of the same carbon number (see CARBON, ACTIVATED CARBON).

Polymeric resins [81133-25-7] are widely used in the food and pharmaceutical industries as cation–anion exchangers for the removal of trace components and for some bulk separations, such as fructose from glucose (87). These resins are primarily attractive for aqueous-phase separations and offer a fairly wide potential range of surface chemistries to fit a number of separation needs. For example, polymeric resins are effective in partitioning by size and molecular weight and may also be effective in ion exclusion (see ION EXCHANGE).

In contrast to these adsorbents, zeolites offer increased possibilities for exploiting molecular-level differences among adsorbates. Zeolites are crystalline aluminosilicates containing an assemblage of SiO_4 and $A1O_4$ tetrahedral joined together by oxygen atoms to form a microporous solid, which has a precise pore structure (88). Nearly 40 distinct framework structures have been identified to date. The versatility of zeolites lies in the fact that widely different adsorptive properties may be realized by the appropriate control of the framework structure, the silica-to-alumina ratio (Si/Al), and the cation form. For example, zeolite A, shown in Figure 9, has a three-dimensional (3D) isotropic channel structure constricted by an eight-membered oxygen ring. Its effective pore size can be controlled at ~3–4 Å. The potassium form, with 3-Å pores, is used for removing water from olefinic hydrocarbons. The sodium form can be used to efficiently remove water from nonreactive hydrocarbons, such as alkanes. The substitution of calcium can provide a pore size that will admit *n*-paraffins and exclude other hydrocarbons.

Large-pore zeolites, X, Y, and mordenites, have pores defined by 12-membered oxygen rings with a free diameter of 7.4 Å. The framework structure of X and Y faujasites sketched in Figure 9 consists of a total of 192 SiO_2 and A102 units. The Si/Al (atomic) ratio for X is generally between 1.0 and 1.5, whereas for Y it is between 1.5 and 3.0. With suitable procedures, Y can be dealuminated to make ultrastable Y with Si/Al ratios exceeding 100. Adsorption properties of faujasites are strongly dependent on not only the cation form, but

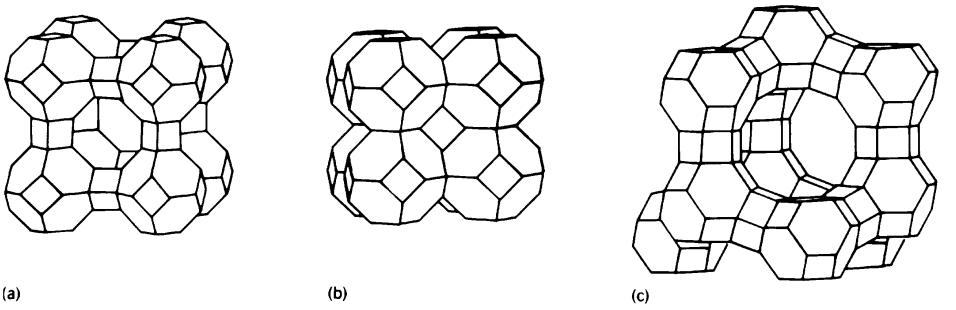

Fig. 9. Three zeolites with the same structural polyhedron, cubooctahedrons. (**a**) Type A, $Na_{12}[(AlO_2)_{12}(SiO_2)_{12}]\cdot 27H_2O$; (**b**) sodalite [1302-90-5]; (**c**) faujasite (Type X, Y), where $X = Na_{86}[(AlO_2)_{86}(SiO_2)_{106}]\cdot 264H_2O$; $Y = Na_{56}[(AlO_2)_{56}\text{-}(SiO_2)_{136}]\cdot 25OH_2O$.

also the Si/Al ratio. The flexibility provided by faujasites in the adsorption of C8 aromatics is shown in Table 1. The selectivity order, from the most selectively adsorbed to the least selectively adsorbed, can be changed significantly by the choice of zeolite properties.

In addition to the fundamental parameters of selectivity, capacity, and mass-transfer rate, other more practical factors, namely, pressure drop characteristics and adsorbent life, play an important part in the commercial viability of a practical adsorbent (89).

6.1. Desorbent. In addition to adsorbent, the desorbent or the eluant plays an important role in the commercial viability of the SMB process. Desorbent is usually physically separable from the product, ie, its boiling point must be either higher or lower by sufficient degrees. Also desorbent selectivity must fall between the two key components which one wants to separate in an SMB mode. The third and equally important property is for the Desorbent to not hinder mass transfer. This can be very important in sterically hindered transfer processes such as in zeolites. For the separation of close boiling isomers the choice of desorbents is limited to the family of molecules which are similar to the key feed components.

7. SMB Applications

UOP has pioneered the use of SMB technology in numerous industrial-scale applications. A good example of the acceptance of SMB technology can be

Table 1. **Selectivity of Zeolites In C_8 Aromatic Systems**[a]

	Adsorbent			
	No. 1	No. 2	No. 3	No. 4
p-xylene	1	2	3	4
ethylbenzene	2	1	4	3
m-xylene	3	3	1	2
o-xylene	4	4	2	1

[a] Key: 1 = most selectively adsorbed, 4 = least selectively adsorbed.

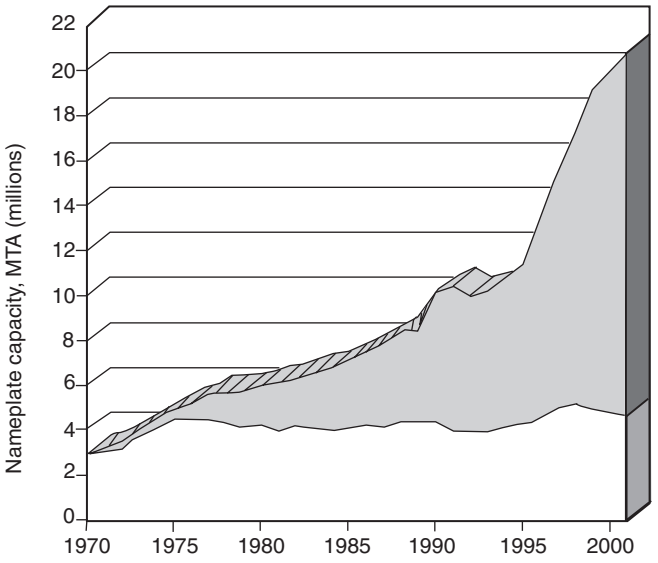

Fig. 10. Technologies for recovery of *p*-xylene: Production capacities since 1970.

found in the recovery of high purity *p*-xylene. Figure 10 (90) shows that liquid-phase adsorptive separation technology has significantly overshadowed crystallization as the preferred means of recovering high-purity *p*-xylene. This is due in large part to the success of the Parex process developed by UOP, but also includes capacity added by others. Hybrid technologies employing adsorption and crystallization can also be practiced (91–95).

8. Adsorptive Separation Technologies

The first commercial application of SMB was through the UOP Molex process to separate *n*-paraffins from branched paraffins, cyclic paraffins, and aromatics. This plant started up in 1960, and its products were used for the manufacture of biodegradable detergents. Since then, at UOP alone, $\sim$ 134 industrial-scale units have been put on-stream in a variety of applications that produce in excess

Table 2. **SMB Sorbex Processes for Commodity Chemicals**

UOP	Processes	units
Parex	*p*-xylene from C_8 aromatics	78
Molex	*n*-paraffins from branched and cyclic	37
Olex	olefins from paraffins	6
Cymex	*p*- or *m*-cymene from cymene isomers	1
Cresex	*p*- or *m*-cresol from cresol isomers	1
Sarex	fructose from dextrose plus polysaccharides	5
MX Sorbex	*m*-xylene/C_8 aromatics	6
total		*134*

Table 3. ***m*-Xylene Separation**

Component	Feed, wt %	Extract	Raffinate wt %
m-xylene	30.5	99.7	0.4
p-xylene	12.9	0.1	18.4
Ethyl benzene	35.8	0.1	51.3
o-xylene	20.8	0.1	29.9
total	*100.0*	*100.0*	*100.0*

of 20 million t/yr of products, worth >10 billion USD/yr. The extent of Sorbex technology commercialization, as of July 2001, is shown in Table 2 (96).

8.1. *m*-Xylene Separation. *m*-Xylene is another important component of the C_8 aromatics stream originating in refineries. It is used primarily to produce Isophthalic acid, which is an additive in the manufacture of PET resins. These "isopolyester" resins are being used in the rapidly growing applications for food and beverage packaging. *m*-Xylene has been traditionally produced via complexation with HF/BF_3. UOP has recently commissioned several MX Sorbex units to recover high purity *m*-xylene by adsorptive separation (Table 3), accounting for more than one-half the world's capacity for *m*-xylene. This technology was recently nominated for the prestigious Kirkpatrick award (97). A sixth unit has been designed.

In addition to the above hydrocarbon separation applications there have been >300 U.S. patents issued for application of SMB in fatty chemicals, carbohydrates, biochemicals, and pharmaceuticals, some of which are given here (98–117).

8.2. Ion-Exclusion Processes for Sucrose. Molasses, which is a by-product of raw cane or beet sugar manufacturing processes, is a heavy, viscous liquid that is separated from the final low grade massecuite from which no more sugar can be crystallized by the usual methods. Molasses has a reasonably high sugar content. The recovery of sucrose from molasses has been the object of intense investigation for >50 years. In 1953, the ion-exclusion process was introduced by the Dow Chemical Company (118). This process, which was developed to separate the ionic from the nonionic constituents of molasses, was based on the fact that, under equilibrium conditions, certain ion-exchange resins have a different affinity for nonionic species than for ionic species.

The ion-exclusion process for sucrose purification has been practiced commercially by Finn Sugar (119). This process operates in a cyclic-batch mode and provides a sucrose product that does not contain the highly molassogenic salt impurities and thus can be recycled to the crystallizers for additional sucrose recovery.

9. Liquid-Phase Adsorption and Separation of Pharmaceuticals and Related Compounds

While adsorption from the liquid phase was originally identified as an important process in biochemical analyses by Tswett at the turn of twentieth century (120), >70 years passed before the power of adsorption as a *process* for production

of pharmaceutical substances and biologically active materials was realized. Since that time, various modes of adsorptive separations have acquired a key role in processes for the production of numerous biologically significant compounds, including:

- Sugars (monosaccharide resolution (121), oligio- (122), and disaccharide purification (123), and recovery from molasses (124,125).
- Amino acids (126) and peptides (127).
- Proteins (128), nucleic acids, and oligonucleotides (129).
- Antibodies [both monoclonal (130) and recombinant (131)].
- Pharmaceutically significant small organic molecules (132), including resolution of enantiomeric and diastereomeric compounds (133–135).

Although many similarities exist with petrochemical applications of adsorptive separations, there are two significant differences in liquid-phase adsorption processes for pharmaceuticals and related compounds. First, the sorbents, which are commonly referred to as "stationary phases" (136), are generally composed of different materials and take slightly different forms compared to the sorbents used in petrochemical applications. Second, the factors that influence the selection of a mode of operation are significantly different in the purification of pharmaceutical and biologically active materials. Therefore, while the available modes of operation are not different, the frequency of application of the various modes differs between the two areas.

In the following sections, we provide a brief overview of sorbents and modes of operation commonly encountered in pharmaceutical liquid-phase adsorptive separations. We illustrate the commercial status of the techniques through an overview of two specific example applications. As a means to provide some guidance for the selection when more than one mode of operation is available, we provide a short discussion of the economics of separation modes at various scales of operation. Finally, we provide a snapshot of the current challenges facing liquid-phase adsorptive separations of pharmaceutically significant compounds.

9.1. Sorbents and Eluents in Pharmaceutical Separations. As in any separation, the liquid-phase adsorptive separation of two or more compounds requires at least one physical property difference that can be exploited. In this manner, a mechanism can be chosen to exploit the desired physical property difference in the molecules to be separated and control the partitioning of the molecules between the liquid and adsorbed phases. The combination of the physical property being exploited and the mechanism through which partitioning occurs, in general, dictates the type of sorbent used to effect the separation.

Generally speaking, sorbents used in separation of pharmaceutical and biological substances fall into two broad categories: solids and gels. Solid packings are based on a polar or inert solid material, usually a metal oxide (eg, silica gel, zirconia, etc), which is typically spherical in shape and between 1 and 100 μ in diameter. Packings of this type are the most common and are routinely applied in the separation of small to moderately sized organic molecules of interest to the pharmaceutical and fine chemical communities. In addition, solid packings with

larger pore sizes have become more widely used in recent years, particularly for the reverse-phase and/or size exclusion purification of peptides (137,138), proteins (138) and oligonucleotides (139). Gel-type packings are typically composed of carbohydrate matrices, with or without cross-linking with agarose or acrylamide (140). These gels are quite soft and can only be used in low- or moderate-pressure chromatography. Gel-type packings are often chosen for the separation of biologics, such as size exclusion-based purification of proteins (140).

The following sections describe most commonly utilized sorbents with a special focus on separation mechanisms used for adsorptive separation processes.

Normal Phase. The designation of normal phase sorbents typically implies the presence of a polar solid-phase material (136). The polarity of the solid phase can be obtained by the use of the solid base itself (eg, silica gel) or through the modification of the solid base with a chemically bonded (bonded-phase chromatography) or a physically adsorbed (liquid-partition chromatography) polar compound. Since the sorbent provides a source of polarity in the separation, the eluents used in normal-phase chromatography are typically non-polar substances slightly modified with components of varying polarity. Separations of this type have been termed "normal" because the solute molecules generally elute in order of increasing polarity.

Reverse Phase. As implied by the name, reverse-phase chromatography provides solute elution in order of decreasing polarity for small organic molecules, which is the opposite of the order observed in normal-phase chromatography. This elution order change is obtained by transposing the polarity of the sorbent and the eluent: In reverse-phase systems, the eluent is usually strongly polar (eg, water) while the sorbent has been modified by a relatively nonpolar compound. Silanes based on trimethyl, butyl, octyl, octadecyl, phenyl, and cyano ligands are the most commonly used. While reverse-phase chromatography packings also exist both as bonded-phase and physically adsorbed-phase materials, application of the bonded-phase packings has dominated since the early 1980s.

Ion Exchange. Electrostatic charge that exists on or near the surface of a solute molecule can be caused to interact with groups, clusters, ligands, or atoms containing the opposite charge on the surface of a solid through the proper choice of conditions and solids (128,141). As the term ion-exchange implies, the fundamental mechanism involves the exchange of a counterion on the solid material with the solute material possessing the same charge as the displaced counterion. Ion-exchange exists in two basic forms, anion exchange and cation exchange. Sorbents in common use for ion exchange are composed of base materials (eg, silica, cross-linked polymers) containing pore diameters ranging from 10 to $>$100 nm that have been derivitized with either positively or negatively charged ligands (142). These ligands can be separated into either strong or weak ion-exchange resins based on their pH susceptibility. In general, strong ion-exchange resins retain their exchange capacity over a wider range of pH, while weak ion-exchange resins have acceptable capacity over narrower windows of pH.

Size Exclusion. Also called gel permeation chromatography, size exclusion chromatography separates solutes solely on the basis of molecular size. As such, it is critical that sorbents used in size exclusion have no physical or chemical interaction with the solutes. Additionally, sorbents that have narrow,

well-controlled and known pore distributions are required for practical and efficient application. Choice of a size exclusion sorbent is typically made by considering the desired pressure of operation as well as the molecular sizes of the solutes to be separated. As described above, low- and moderate-pressure applications can use either carbohydrate (soft-gels) or carbohydrates cross-linked with agarose or acrylamides, respectively. For high-pressure applications, size exclusion chromatography typically employs a spherical silica support of 5–10 μ in diameter possessing a controlled pore size distribution. The surface area of these silica packings is typically modified by a covalently bonded neutral molecule to eliminate surface silanol groups (140).

9.2. Recent Advances in Sorbent Materials. Hjerten and co-workers (143) showed that certain types of acrylamide gels, prepared directly within the column, can be compressed above the typical operating pressure yielding aggregated polymer gels with small (3–4 μ) channels between particles. These materials have good dynamic capacities that are maintained as flow rates are increased, allowing significant decreases in analysis time with no loss of resolution. While analytical columns of this type are available, preparative and process chromatographic application has yet to occur even though the promise of these materials for high-throughput separations is quite high.

Macroscopic rods of silica, formed by a reactive molding technique, have been created that contain micron-sized pores with shallow mesoporous "pockets" in the 10–30 nm range (144). The ready access of these shallow pores from the relatively small flow channels allows even the most rapid adsorption–desorption phenomena to occur in the absence of mass transfer limitations. Recently, these materials have been made available at the preparative or semiprocess scale by E. Merck, although published details of their application is presently limited.

9.3. Sorbents, Eluents, Solubility, Method Optimization, and Modeling. While limited sample solubility often can be overcome through a variety of techniques for analytical separations, the cost-effective application of most preparative- and process-scale separations requires moderate (>20 mg/mL) solubility in the eluent. As such, method development for process separations is more demanding, requiring good chromatographic performance with the least complex, most readily available eluents in which the solute components are readily soluble. It must be recognized that optimization of process chromatographic methods, regardless of the mode of operation, requires attention to many such details and, eventually, requires an iterative process often full of compromises. Given these important criteria, the significant advancements over the past decade made in the area of modeling the modes of preparative and process adsorptive separations are quite easy to understand (145–148). Nonetheless, it has become common-place, and nearly necessary, to employ either short-cut (149,150) or rigorous calculation models (151,152) to properly optimize adsorptive separations of pharmaceutical and biological interest.

10. Equilibrium Theory

An improvement over the traditional McCabe–Thiele analysis for adsorptive separations can be found within the equilibrium theory model (147). While this

model does not include the effects of axial dispersion nor does it address the potential limitations imposed by mass-transfer resistances, the impact of adsorption equilibrium phenomena are adequately represented by this model. Analytical solutions have now been obtained for a variety of cases and subcases utilizing a variety of basic isotherm equations and assumptions (153–156). Details of the solution to these design problems have been ably covered by Morbidelli and coworkers (152–156) and Chaing (150,157). Only the basic aspects results of this theoretical analysis are presented here.

For a true moving-bed (TMB) countercurrent system at steady state, the equilibrium theory analysis identifies a series of j key design parameters defined by notation L_k, where j is the number of sections within the system. These design parameters, commonly referred to as zone ratios, are defined as the ratio of the net fluid phase flow rate and the net adsorbed phase flow rate within each section (147). Please note that various authors use various numbering schemes for the sections of the TMB/SMB process. Here, we number the zones of a TMB/SMB process in a manner that is consistent with Figure 1.

Equilibrium theory yields a specific set of key operating parameters that will accomplish the complete separation (two pure products) given a well-defined isotherm, the composition of the feedstock, and knowledge of certain physical properties of the sorbent, feedstock and desorbent (147). Provided that certain criteria with regard to L_3 and L_4 zone ratios are met, the complete separation region can be visualized in the two-dimensional (2D) space defined by the L_1 and L_2 design parameters as illustrated in Figure 11.

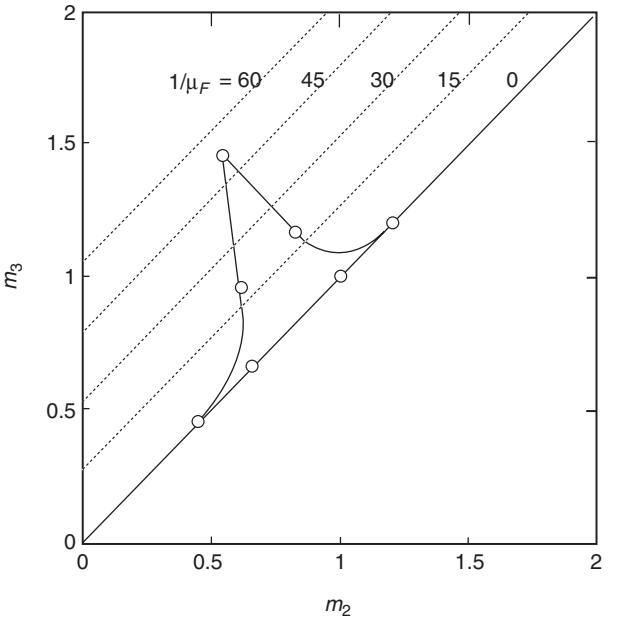

Fig. 11. Region of complete separation of in the L_1–L_2 plane using a two-component feed and a Gurvitsch isotherm. The dashed lines are lines of constant productivity, which increases as you move away from the diagonal. Reproduced with premission of the American Institute of Chemical Engineers.

Due to the shape of this allowable operating region, equilibrium theory has often been referred to as "triangle theory" within the literature. The shape of this operating region is governed by the type of adsorption isotherm selected as well as the relative strengths and, in some cases, adsorption capacities of the various components. Equilibrium theory has been successfully applied to several experimental systems [eg, see Migliorini and co-workers (155) and Francotte co-workers (155)].

11. Modes of Adsorptive Separation

While the applications of liquid-phase adsorptive separations in the petrochemical industry have tended toward the use of continuous processes, the same cannot be said for pharmaceutical and biomolecule separations. In fact, in contrast with the availability of continuous processes for >40 years, only within the past 10 years have modes of operation *other* than batch adsorptive separations been described in the literature. The potential reasons for the slow progress of continuous adsorptive separation processes (indeed, continuous process *in general*) in the pharmaceutical industry are potentially many. However, three particular hurdles to application can be readily identified.

First, and probably foremost, is the tremendous difference between the petrochemical and pharmaceutical applications "objective functions" that are used to determine the optimum process choice. Petrochemical process options tend toward minimization of the cost of manufacture (COM), while COM is rarely a substantial portion of the overall cost of development of a pharmaceutically important substance. This finding is especially true as the location of the separation in the production sequence moves further toward the active pharmaceutical ingredient (API). In addition to cost differences, different valuations exist between the two sectors for such fundamental parameters as time-to-market and risk-avoidance. Finally, while petrochemical processes tend to be carried out at high volume in dedicated facilities, the low volumes and product turnover experienced in the pharmaceutical industry favor manufacturing through general rather than specialized pieces of equipment.

A second governing issue is the generally greater complexity of the most common adsorptive separations in the pharmaceutical and bioprocess industries as compared to the general chemical industry. For example, most adsorptive separations in the petrochemical industry can be treated as binary separations, while the same is certainly not true for purification and separation of most pharmaceutical applications. A third seminal hurdle to be overcome by continuous adsorptive separations in pharmaceutical and biomolecule applications are the issues associated with validation and regulation, particularly in the application of current good manufacturing practices (cGMPs) to continuous separations.

These and other critical issues have led to the present situation in which batch adsorptive separation is preferred in pharmaceutical and biomolecule processes. This situation is, however, changing rapidly with a noticeable acceleration in the past 5 years. While batch adsorption processes will continue to be important for manufacturing of biologically important materials, there will continue to be cases which are particularly well suited to continuous processes,

and these instances are likely to increase in frequency with each successful application.

The following sections briefly describe the different process modes of adsorptive separation as they are practiced in the pharmaceutical and biomolecule sector. As considerable overlap exists between the operating modes with the previously described petrochemical applications, only details that are fundamentally different are mentioned. Where relevant, mention has also been made of commercial or near-commercial examples of practical interest.

12. Batch Processes

Batch processes are relatively abundant in the purification and separation of pharmaceutically important substances, particularly in the areas of peptide (127), proteins (128), and oligonucelotides (129). In the most common applications, periodic injections are made on a column containing the appropriate sorbent media, and the eluent composition is either held constant (isocratic elution) or programmed (gradient elution) while the solute components are separated and the appropriate portion or portions of the purified effluent is collected. This can be followed, if required, by a column cleaning–equilibration step.

One commercial example is the purification of synthetic oligonucleotides for use as antisense drugs. Isis Pharmaceuticals, Inc. (Carlsbad, Calif.) has recently launched an antisense oligonucleotide drug that utilizes a single-column batchwise purification of a synthetic oligonucleotide late-stage intermediate (139), and three practical approaches to the postsynthesis purification have been recently described (158). One such scheme is a reverse-phase purification using either silica or polymer supports derivitized with octadecylsilanol (ODS) and weakly buffered eluents such as sodium- or ammonium acetate (158). In this purification scheme, the particular protected phosphothioate N mer of interest is separated from earlier eluting chain-growth failures, unattached protecting groups, unprotected oligonucleotides, and oligonucleotides that are smaller than the target ($<$N mers). In addition, some later eluting impurities are present and must be excluded from the purified material. An anion-exchange chromatography method may follow the reverse-phase method described above, resulting in $>$96% pure oligonucleotide (139,158). This combined process has been used by Isis Pharmaceuticals for the production of Vitravene (fomivirsen sodium), which was the first antisense drug approved for market by the U.S. Federal Drug Administration (FDA) (139,158,159). Annual cGMP production of antisense oligonucleotides is expected to reach 1 ton within the next few years (160).

13. Cyclic Processes

Similar to batch separation processes, the pharmaceutical and biomolecule separations industry defines cyclic processes as those in which solute material is recycled, with or without fresh solute material, back to the sorbent bed for further processing. Preparative and process separations have used eluent recycle closed-loop recycle (161–163) to improve eluent efficiency and/or the number of

theoretical plates available for separation. If fresh solute were to be sent to the column along with the recycle solute, the two solute materials would be well mixed (162). In a recent advancement of this process, Grill (164) introduced a closed-loop recycle technique in which the chromatographic profile of the recycled solute is maintained and the fresh solute is injected at precise, optimized location while avoiding significant mixing. This technique has the advantage of further increasing the apparent number of theoretical plates for the separation through maintenance of the original profile. Although this technique holds promise, it has been shown to provide sorbent efficiencies that are superior to batch process, but inferior to SMB (165,166). Likewise the process flexibility is somewhat > SMB but inferior to that of batch processes.

Japan Organo Co. has introduced a "pseudo-SMB" process that uses column effluent recycle technology along with period introduction of both solute components and eluent (130). A recent introduction, the capabilities, advantages, and limitations of this process have not been fully explored or published, however, it appears to offer some of the same benefits of the steady-state recycle technique described above while maintaining some of the flexibilities of the batch processing, including the ability to perform ternary and higher order separations (167).

14. Continuous Processes

Although it had long been established as a viable, practical, and cost-effective liquid-phase adsorptive separation technique, the pharmaceutical and biomolecule separations community did not show considerable interest in SMB technology until the mid-1990s. In 1992, Daicel Chemical Industries, Ltd.(168,169) first published the resolution of optical isomers through SMB. Since that time, >600 articles, patents, books, and reviews on the application of SMB to pharmaceutically important compounds have been published. Though resolution of enantiomers is only one such application of SMB in pharmaceuticals and biopharmaceuticals, it has quickly become an area of significant focus. For example, ~25 companies, universities, and institutes worldwide had installed commercial or pilot-scale capacity for SMB applications in the pharmaceutical sector, with a particular emphasis on resolution of chiral products.

In early 2002, Forest Laboratories, Inc. (New York) announced that the U.S. FDA had issued an approval letter for the use of the compound escitalopram oxalate in treating major depressive disorder. Escitalopram oxalate, a selective serotonin reuptake inhibitor, is the single-isomer version of the successful Celexa antidepressant and is licensed from H. Lundbeck. It is well known within the industry (170) that a critical step in the production of escitalopram oxalate is the resolution of the (*S*)-enantiomer of citalopram from the racemic mixture by SMB adsorptive separation. This success is likely to raise awareness and application of SMB in pharmaceutical industries. Indeed, the Belgian pharmaceutical company UCB Pharma is presently exploring (170) the potential use of SMB for enantiomeric resolution and ultimate commercial production of a pharmaceutical compound.

Enantiomeric resolutions are only one area of potential application of SMB in pharmaceutical and biotechnology manufacture. Indeed, the voluminous

literature is filled with other applications, including the purification of paclitaxel (171), betaine recovery from beet molasses (172), antibiotics (173), and azeotropic protein separations (174). The later two cases required the use of SMB in a relatively new mode, that of providing an eluent composition gradient, and theoretical treatments of this new method are now beginning to appear in the literature (174–176). It is therefore likely that the most significant contributions of SMB in the pharmaceutical and biotechnology sectors are yet to be discovered.

The dynamic field of continuous chromatography is itself evolving at a rapid pace. New hardware, new sorbents and new methods of operating are being identified and published at a significant rate. For example, a variation of SMB has been demonstrated in which the positions of the net fluid flows to and from the system are changed independently rather than simultaneously (177). It has been reported that this modification allows, in some cases, an increased sorbent and eluent efficiency while potentially requiring less hardware.

15. Economics of Pharmaceutical Separations

Schmidt-Traub and co-workers (178) recently performed a detailed economic comparison for the enantiomeric separation of a late-stage pharmaceutical intermediate through batch and SMB chromatography. The authors examined the cost of separation for optimized batch and SMB operations, and compared them on the basis of the cost of capital, operation, sorbent, eluent, and lost crude. The calculations were prepared at two different production levels, 1 and 5 MT/year. Although some of the cost factors assumed by the authors are quite low for operation in a cGMP environment, the results, shown in Table 4, are instructive.

As expected, costs for SMB separations are equivalent or superior to batch chromatography at these scales, with the benefit to SMB operation increasing as the production scale increases. Two unexpected results were obtained, however. First, the cost of the sorbent material was, on average, a lower cost than has been anticipated by other, less rigorous investigations. Second, the authors suggest that the cost contribution of eluent is actually higher in SMB operation than for batch operations. Although some of the authors' conclusions may be biased

Table 4. **Comaprison of SMB and Batch Chromatography for Enantiomeric Purification of a Pharmacuetical Intermediate**[a]

	SMB		Batch	
Contribution (% of total)	1 MT/a	5 MT/a	1 MT/a	5 MT/a
capital	18.9	9.2	8.3	4.2
operation	8.6	2.1	8.3	4.2
eluent	64.1	78.4	49.1	55.3
sorbent	8.4	10.3	21.0	23.6
lost crude			13.3	15.0
total cost ($/g)	*2.11*	*1.72*	*2.18*	*1.94*

[a] Ref. 178

by the particular separation example chosen, the conclusions offer a starting point for future, detailed investigations of the optimized cost comparisons of these operations.

16. Outlook

Liquid adsorption processes hold a prominent position in several applications for the production of high purity chemicals on a commodity scale. Many of these processes were attractive when they were first introduced to the industry and continue to increase in value as improvements in adsorbents, desorbents, and process designs are made. The Parex process alone has seen three generations of adsorbent and four generations of desorbent. Similarly, liquid adsorption processes can be applied to a much more diverse range of problems than those presented in Table 2.

A surprisingly large number of important industrial-scale separations can be accomplished with the relatively small number of zeolites that are commercially available. The discovery, characterization, and commercial availability of new zeolites and molecular sieves are likely to multiply the number of potential solutions to separation problems. A wider variety of pore diameters, pore geometries, and hydrophobicity in new zeolites and molecular sieves as well as more precise control of composition and crystallinity in existing zeolites will help to broaden the applications for adsorptive separations and likely lead to improvements in separations that are currently in commercial practice.

With the increased speed of discovery in the area of pharmaceuticals and biotechnology, SMB does offer an attractive alternative to conventional batch chromatography separation methods. SMB overcomes the general view of batch chromatography as low throughput, low yield, and high cost process and will likely find increased acceptance as a unit operation in both the discovery as well as production phase of drug development.

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