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CHEMICAL AND BIOCHEMICAL SEPARATIONS USING PREPARATIVE AND LARGE SCALE BATCH AND CONTINUOUS CHROMATOGRAPHY

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SUMMARY

This chapter surveys the progress made during the last thirty years in scaling-up the analytical chromatographic process into preparative and production scale processes for the continuous separation of gas or liquid mixtures. The different design approaches are reviewed and some results from their applications are included to enable some comparisons between the various methods to be drawn. Batch, continuous counter-, cross- and co-current systems have been considered, ranging from small scale to industrial size systems. In addition to chromatographic separators, part of this chapter is also devoted to the use of these systems as chromatographic reactor-separators. This is an important extension to the application of the chromatographic principle, since it opens up new horizons and

provides the chemist and the engineer with a new tool in applications where the removal of a reaction product from the reaction mixture causes a shift on the equilibrium of a reversible reaction and results in increased conversions. It has also been shown that by the removal of a reaction product which is acting as an acceptor can improve the product yield of polymeric biochemical reactions. Chromatographic refining is no longer just an analytical tool but has become an important unit operation which one cannot afford to overlook when considering ways of separating a given chemical or biochemical mixture or when confronted with both reaction and separation problems.

1.0 INTRODUCTION

Chromatography can be defined as the unit operation where the separation of solutes is brought about due to the differential migration of the solutes through a system of two phases, the stationary (column packing) and the mobile phase (a suitable liquid in the case of liquid chromatography).

One of the prime tasks of the chemists has been the separation of individual components from mixtures. Some of the methods used by chemists are old and have been known for centuries, i.e. crystallisation, precipitation, sedimentation, extraction, and distillation. Although the significance of these methods is important

in the separation field, they have increasingly been found to be less useful for the solution of new separation problems encountered by chemists and even more so by biochemists, for example, in the separation of amino-acids, proteins, dyes, complex hydrocarbons, nucleosides, nucleotides, and many other heat and process sensitive substances. Therefore, this led to the development of more effective separation methods and chromatography is one of the most popular due to its increased separation power and its wide versatility.

The chromatographic principle has been employed since the turn of the nineteenth century, i.e. by employing the absorptive capacity of certain types of carbon for the purification of beet juices[1], the capillary analysis work of Runge in the middle of the last century using coloured chemicals on filter paper which has been described in detail by Hais and Macek[2]; and the ion exchange studies of Eichhorn[3] and Boedecker[4] and the application of natural and synthetic ion-exchangers in sugar production patented in 1896[5]. However it was not until 1906 that the work of Tswett[6] demonstrated its importance. In his studies he investigated the separation of plant pigments using a column packed with calcium carbonate, and after observing that the mixture was separated into a series of green and yellow bands he defined the process as "chromatography" a Greek term meaning "colour writing".

The significance of his work was not realised until 1931 when Kuhn, Winterstein and Lederer[7] published the results of their chromatographic studies. In 1938 liquid chromatography was

introduced by Steiger and Reichstein[8], and Tiselius[9] from 1940 to 1943 investigated the technique of frontal analysis and displacement development. In 1941 Martin and Synge[10] introduced partition chromatography using silica gel, thus extending the applications of chromatography to the biochemical field. Another tool for the biochemist was the development of paper chromatography in 1944 by Martin and co-workers[11].

A major new field of separation was created by the introduction of gas-liquid chromatography in 1952 by Martin and James [12], and for their contribution to chromatographic science,they were awarded the Nobel Prize. The inception of gas chromatography triggered various researchers around the world into developing the chromatographic principle further both at the analytical level and by scaling-up the process for preparative and production scale use.

Although continuous development work has been performed in all chromatographic modes, the literature shows that gas chromatography was more popular during the 50's and 60's at the analytical and production scale levels whilst liquid chromatography has taken over since the beginning of the 70s especially after the restructuring of the USA's sweetener industries to include high fructose corn syrups produced by the enzymatic conversion of maize.

Chromatography has now gained extensive recognition as a powerful analytical tool, and in the appropriate form has found its

way into industry for the quality control of raw materials, intermediates and products, and also for process control purposes. Production scale chromatography already enjoys applications in the hydrocarbon and carbohydrate fields and commerical plants with columns 3.6 m dia x 12 m high have been built[13]. Although the chromatographic innovation offers high separation potential, it is not energy intensive, does not involve any phase change, and is very versatile, but even so has not had the large industrial impact that might have been expected. It is believed, however, that most of the major chemical industries establishments are now involved directly or indirectly with chromatography and it is now only a matter of time before the industries' conservatism is overcome and many more large-scale processes are built. One can also argue that the "newer" industries, especially the ones in the biotechnology field, will lead the way.

In selecting the chromatographic type system for larger scale chemical and biochemical separations, as the throughput increases it is not only important to design the most efficient separation system, but one must design the most efficient system at minimum capital and operating costs and maximum throughput. Different scale-up approaches have been followed over the last three decades and these fall into two main categories, batch and continuous.

In batch systems a direct scale-up of the analytical process is attempted by using larger diameter packed beds incorporating in some cases a bafffling device to enhance radial and minimise

longitudinal mixing. In the continuous systems a large number of approaches exists and in all of them the stationary phase moves counter-currently, cross-currently or co-currently to the movement of the mobile phase. This stationary phase movement either takes place physically or is simulated. The various scale-up approaches will be reviewed in this chapter and some indication will be given about their scaling-up potential and reference will be made to industrial applications.

So far chromatography has been used as a separation process. This chapter, however, will also describe its application as a dual mode unit operation, namely as a combined reactor-separator.

2.0 BATCH CHROMATOGRAPHIC PROCESSES

The scaling-up of chromatographic processes over the last two decades has mainly favoured the batch mode primarily due to the simplicity of the operation.

During the 1960`s ABCOR (Mass, USA) pursued the scaling-up of batch gas chromatographic systems. They began by offering standard plants of different sizes with columns up to 4 ft (1.3 m) diameter. The stainless-steel plants were designed to be as versatile as possible and were adequately instrumented and automated. The model GC-50 consisted of 15 cm id columns, while the GC-100 system had two 33 cm id columns which could be interconnected in

series to form a batch system of up to 6.6 m long. These systems were targeted towards the separation of chemicals which were not readily or economically produced by any other method, such as flavours and fragrances, petrochemicals (i.e. pentene isomers) and pharmaceuticals. A 1.3 m (4 ft) diameter and 3 m (10 ft) high batch system was built to separate alpha- and beta- pinenes at an estimated annual throughput of 900 tonnes and at 1968 prices cost about $160 000[14]. For the commercial separation of the aromatic isomers m-xylene and p-xylene Abcor employed two 4.6 m id x 4.6 m long gas chromatographic (GC) columns and a liquid chromatographic system (LC) consisting of two 4 m id x 8.6 m high columns. The columns in the two systems were alternately fed, and the GC and LC systems could operate independently with a combined production rate of 50000 tonnes/year. The 1969 capital costs for the GC and LC systems were $1.53million and $1.1million, and the annual operating costs $0.6million and $0.5million respectively[15].

Elf-Aquitaine and the Société de Recherches Techniques et Industrielles (SRTI) in France have also shown an active interest in batch chromatography, and by 1980 over 20 plants had been built around the world. In October 1979 a production scale Elf-SRTI unit went into operation at SCM Corporation Glidden Division plant in Jacksonville, Florida, consisting of a 0.4m diameter by 1.5 m long GC columns capable of handling a throughput of 130 ton/yr, and producing 90 ton/yr of pure product. The system was used to purify perfume ingredients and flavour chemicals manufactured from terpene feedstocks at purities exceeding 99%[16]. In an alternative

chemical field Elf's N-ISELF process has been used to separate normal paraffins from a light naptha feed. It employed molecular sieves and the normal paraffin product was used as a petrochemical feedstock, and as it was rich in isoparaffins a high octane fraction in gasoline production. The system is reported to handle hydrocarbons ranging from C_4 to C_{10} producing paraffins from 80 to 99.8% pure. Elf decided to build a 100000 ton/yr unit at Donges, France, producing a fuel base and an n-paraffin cut that would serve as a feedstock for an isomerisation unit converting n-paraffins to iso-paraffins[17]. The plant was due to start up in 1982 but the authors believe it has not been built. The company also offers standard units which are fully automated for the purification of flavours and fragances, with capacities from 3 to 300 ton/yr, purities of over 99.9% and yields better than 95%[18].

It is the Finnish Sugar Co. Ltd., that can be considered as the leader in the batch LC field and especially in carbohydrate separations. In 1962 the company decided to become committed to the scaling-up of batch chromatographic processes and to date they have designed and built many systems throughout the world and claim they to have the largest chromatographic plant in use. They specialise in the desugarisation of beet molasses, recovering sucrose by employing mainly the ion-exclusion effect, and in the production of high fructose corn syrups by ion-exchange on Ca^{++} charged cross-linked polystyrene resins. In 1975 they installed the then largest batch chromatographic molasses separation plant in the world, consisting

of one 2.7 m id x 6 m high column, recovering up to 95% of the sugar in molasses and obtaining purities of up to 92%[19]. In 1983 a new plant was completed for Amino GmbH in Frellstedt, Germany, for the recovery of beet molasses, at a reported cost of $7.6m (1983). Seven resin filled 3.6 m id x 12 m high columns were used in the separation step, processing 60000 tons/yr of molasses, and the typical product concentrations were about 21% w/v, 9% w/v and 5% w/v sucrose, non-sugars and betaine respectively[20]. It has also been reported[20] that they have installed a Xyrofin plant in Thomson (Ill., USA) producing over 13000 tons/year of crystalline fructose from corn-syrup. High glucose syrup is isomerized to a 42% fructose solution by passing it through reactors containing immobilised glucose isomerase, and then separated in a total of 17 batch chromatography columns.

Finnish Sugar have also developed preparative and commercial scale systems for the production of mannitol, xylose, betaine, speciality sugars, aldonic acids and amino-acids such as alanine, valine, leucine, etc.

In the mid-seventies Munir of Suddeutsche Zucker AG (Germany), reported a new process for the separation of beet or cane molasses[21, 22]. Three columns each of 1 m id x 6 m high were used, and were packed with a 4% cross-linked Lewatit TSW 40 (Bayer AG) resin in the Ca^{2+} form. The main objective of the process was the recovery of sucrose, but they claimed that the

molasses can also be used as a source for recovery of certain amino-acids. Molasses at 50% w/w were injected at feed charges of up to 6% of the total bed volume. A repetitive product splitting and redirection operation was employed giving a 95% sugar recovery and a 90% pure product containing up to 11% dry matter.

The Illinois Water Treatment Co. (USA) has been active in the sweetener industry over the last 30 years. In conjunction with Finnish Sugar they have used a system for the desugarisation of molasses consisting of a number of vertical columns operating continuously. They have developed their own way of switching the feed and eluent inlet and product outlet points but, unfortunately, there is not enough information available about the system, its operation and its commerical viability.

Pharmacia Fine Chemicals (Sweden) market purpose-built batch chromatographic columns of various sizes. Among the various packing materials they offer, they promote a cross-linked dextran polymer gel under the trade name of Sephadex. Sephadex packed columns of up to 180 cm diameter have been used for the separation of milk protein from whey, the fractionation of proteins and amino-acids, the preparation of enzymes, and the purification of penicillins from high molecular weight impurities[23].

Over the last five years or so, production scale high performance liquid chromatography (HPLC) has become available, giving over

twenty times the capacity of previously employed HPLC systems. Such production scale HPLC equipment are: the series 300 LC Elf Aquitane system consisting of a 30 cm id x 1.5 m long column operating at 5170 KNm^{-2}; the Whatman Magnum which has a 15 cm id x 2 m long column and operates at 6900 KNm^{-2}; and the Waters Kiloprep system consisting of a 15 to 20 cm id column 2 m long in 3 segments operating at 3450 KNm^{-2}, used particularly in the isolation and purification of peptides[24].

It is also worth mentioning the Asahi process (Asahi Chem. Ind. Co. Ltd.) for separating p-xylene and ethylbenzene by employing a Zeolite-desorbent system of excellent selectivity and absorptivity[25]. The company claims that their developments in column packing and design makes the process highly economical for new plants and also could increase capacity and produce p-xylene and ethylbenzene simultanously at existing plants. The process was ready for commercialisation five years ago, but there is no further information available.

During scaling-up dynamic similarity must be maintained between small and large columns. This can be achieved by keeping the Reynolds number the same in each column. To maintain the resolution the same the adsorption capacity per unit volume of packing and the column voidage should also be kept the same. Therefore selecting the right type of packing and employing the correct method of packing is very important. The mean particle size

of the packing is chosen according to the distribution coefficients of the components to be separated, and for a good separation the size range must be very close, i.e. over 95% of the resin must be within 20% of the mean particle size. Maintaining the same packing eficiency is very difficult during scaling-up, and although the slurry packing technique is very popular the process of packing still remains an art.

During scaling-up, problems associated with uniform liquid distribution result in flow irregularities, such as "tailing" and "finger formation". This problem was apparent from the early days of large scale gas chromatography and a variety of column baffle systems were introduced to enhance radial mixing and to maintain a narrow band profile lying in an horizontal plane.

Although this baffle arrangement has been found to be effective it presents substantial problems when it comes to backwashing, regenerating or repacking the column, and it also is very difficult to accommodate any swelling or shrinking of the resin bed. Recent LC practice, however, has changed towards baffle free systems, flow uniformity being achieved by optimising the flow rates, temperature, and column solute concentration, thus controlling viscosity and density gradients.

Alternative ways of maintaining flow uniformity are by using a number of shorter columns instead of a long one, or by saturating the column with the solution which is to be separated.

To increase throughput and optimise the total volume of packing available, the repetitive feed injection technique is employed whereby by proper timing the leading edge of the fastest moving component from the second injection comes out just after the tailing edge of the slower moving component of the first injection, or they overlap each other to a predetermined extent. This overlapped fraction is then recycled; recycling of up to 40% of the feed is commonly practised.

3.0 CONTINUOUS CHROMATOGRAPHIC PROCESSES

The inherent advantages of continuous operation, namely the increased flexibility, unattended operation, constant product quality, limited or no recycling, and the better utilisation of the available mass-transfer area has led many researchers to the development of such systems of different configurations.

To increase the throughput, high feed concentrations are used and to approach a fully continuous counter-currrent operation an increased number of short columns or compartments is often employed .

This increased number of columns and the counter-currrent flow in particular minimises the disturbances caused by density gradients and reduces flow irregularities.

The continuous mode of operation was introduced in the late 1950's and has taken several forms. The various processes generally fall

into the following three categories, counter-current, cross-current and co-current, defined according to the relative movements of the mobile and 'stationary' phases.

3.1 Counter-current Processes

The potential of counter-current processes relative to conventional batch can be illustrated by the help of Figure 1 which presents the idealised solute concentration profiles for a binary separation.

To obtain high purity products in batch processes either the eluted components must be fully resolved, i.e. very long columns, or the central 'valley' or overlapping fraction must be removed. In production scale batch systems the repetitive feed injection and continuous recycling of the overlapping parts are employed, resulting in up to 40% recycling of the injected sample.

In counter-current processes the solute concentration profiles need only to be partially resolved within the chromatographic column to permit collection of high purity products at the system outlets. Therefore, the entire separating power of the system is used effectively permitting severe overloading by batch co-current standards, enabling higher throughputs per unit volume of resin. Selecting the proper flow rates is critical in continuous systems in order to achieve the solute with the least affinity for the stationary phase to progress preferentially with the mobile phase while

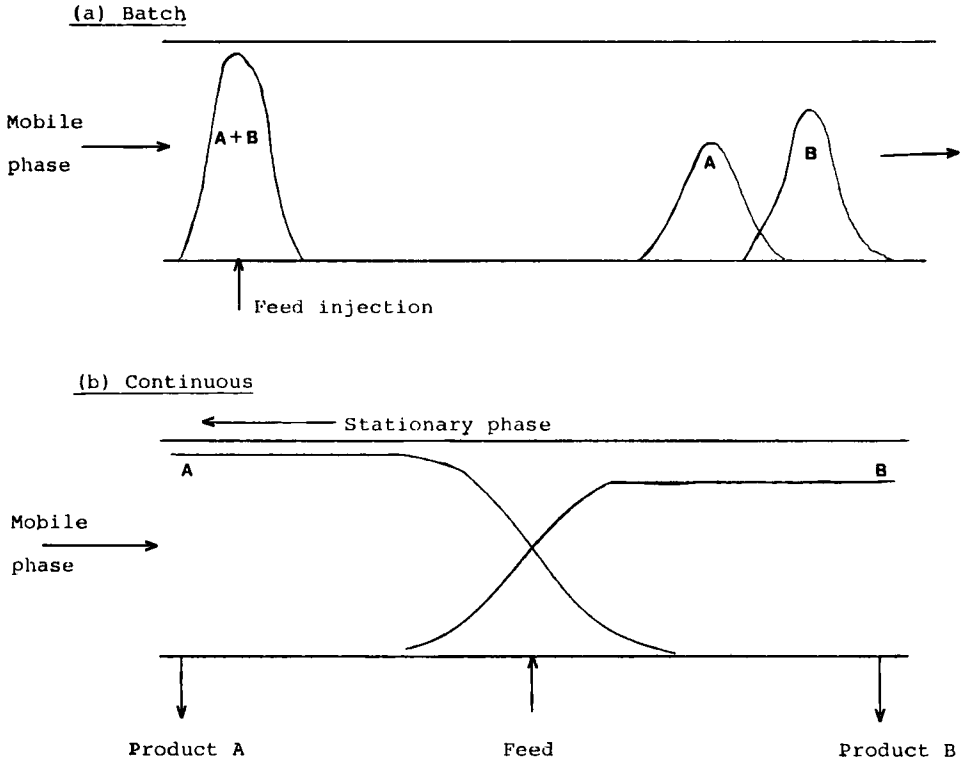


FIGURE 1
Batch and countercurrent continuous chromatography

allowing the more strongly absorbed solute to move with the stationary phase.

The disadvantage with the counter-current systems is that they can only perform a two component or two different fraction separation at a time, while with co-current batch and cross-current continuous systems a multicomponent separation is possible at the same time. The development of counter-current chromatography has been

carried out along three different routes over the last 25 years, depending on whether the bed or the column have been physically moved or the stationary phase movement simulated by some mechanical means.

3.1.1 Moving Bed Systems

These systems were the first type of counter-current chromatographic systems and were employed industrially almost forty years ago to perform gas separations. With this type of system the packing flowed under gravity while the mobile phase passed in the opposite direction in a vertical column. The feed to be separated was pumped continuously into the centre of the column, the least strongly absorbed component being carried upwards and exiting from the top of the column whilst the more strongly absorbed component moved downwards with the packing being stripped at the bottom part of the column (Figure 2).

Probably the earliest of such large-scale processes was the Hypersorption Process[26,27] developed by the Union Oil Co. (California, USA). It used an activated-carbon absorbent flowing continuously downwards through a rising gas stream containing methane, hydrogen, about 6% ethylene and other gases more volatile than ethane. The column was 26 m high and 1.4 m in diameter. A unit built for the Dow Chemical Co. had over 500000 m^3 capacity of gas per day. However, the process proved to be less economical

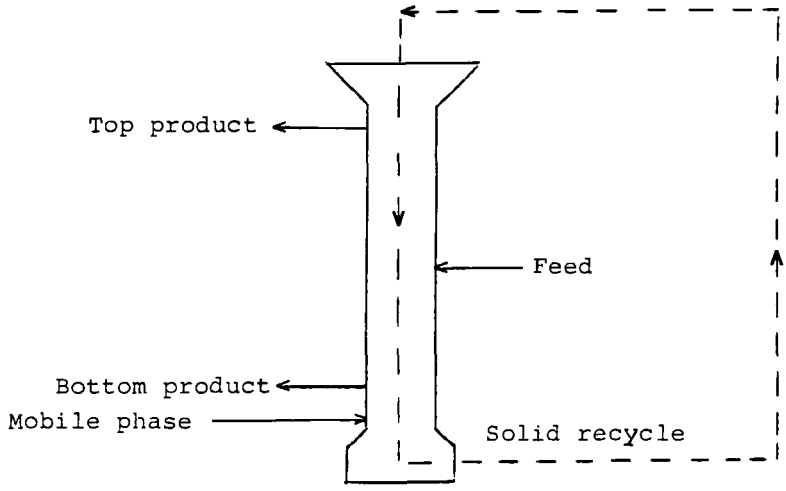


FIGURE 2
Moving bed chromatographic system for binary separation

than low-temperature distillation and is no longer in operation. Several gas-liquid variations of this chromatographic technique have been reported. Schultz[28] used a 0.01 m id x 1 m long column packed with Sterchamol particles coated with 30% dibutyl phthalate and separated a mixture of cis- and trans-butane-2 at feed rates of 78 $cm^3\ h^{-1}$ with product purities of over 99.3%.

Clayer *et al.*[29] separated the hydrogen isotopes protium and dentrium using a 2 cm diameter column and flowing silica gel particles. Protium was withdrawn at the top and dentrium was stripped at the bottom either by temperature rises and using helium or by using nitrogen as the displacing gas. Clayer[30] also carried out the separation of C_4 hydrocarbons in a similar system without

the use of an inert mobile phase. Using dinonyl phthalate as the stationary phase isobutane, butene-2, n-butane taken in binary pairs gave products in these studies which were claimed to contain less than 50 ppm of impurity. Husband *et al.*[31] had used a 2.5 cm id column earlier and separated benzene-ethyl alcohol mixtures on activated carbon at throughputs of up to 720 cm^3 hr^{-1}.

Philips Petroleum[32] used a 15 cm id x 254 cm long column and 1.5 mm firebrick spheres coated with dioctyle phthalate as the falling phase and hydrogen as the mobile phase to separate successfully benzene/cyclohexane mixtures at 85 °C and throughputs of up to 225 cm^3 min^{-1}.

Fitch *et al.*[33] separated diethyl ether, dimethoxy methane and dichloromethane binary mixtures by employing a falling bed of Celite impregnated with dinonyl phthalate.

Pritchard *et al.*[34] used a similar system and employed a 2.5 cm id by 130 cm long separating section, and a 10-22 mesh chromosorb P packing impregnated with 20% w/w dinonyl phthalate. Nitrogen was used as the carrier gas. Separations of equimolar mixtures of diethyl ether and dimethoxy methane at feed rates of 5 cm^3 h^{-1} and product purities in excess of 99.9% were obtained.

Barker and co-workers[35-38] experimented with a 2.5 cm id x 2.79 m high vertical column, with a downward falling chromatographic

paking coated with a relatively non-volatile liquid phase. They used the above apparatus to separate successfully the azeotropic mixture benzene (b.pt. 80.1 °C) and cyclohexane (b.pt. 80.7 °C) using a polyglycol derivative (polyoxethylene 400 diricinoleate) as the polar stationary phase adsorbed on to 1680-841 μm particles of C22 Sil-0-Cel firebrick, The column efficiency in terms of transfer units gave HTU_{OG} values of between 9 and 10 cm.

The apparatus was later modified[37,38] to be used with ternary hydrocarbon mixtures by introducing a side arm containing a fresh flowing stream of packing between the bottom stripper and the feed inlet (Figure 3).

When 12.6 $cm^3\ h^{-1}$ of an equivolume mixture of cyclohexane, methylcyclohexane and benzene were fed in the system, 98.7% pure cyclohexane and 99.5% pure methylcyclohexane was obtained from the top and the side draw outlets, while the bottom product contained 26.4% methylcyclohexane and 73.6% benzene.

Kuhn *et al.*[39] utilised the temperature dependence of the partition coefficients in flowing liquid columns containing steel spirals. By having sections of the column at different temperatures and constant gas and liquid flow rates, the different components were collected at different places in the column depending on the partition coefficient values. The column used consisted of five sections maintained at different temperatures which decreased along the column. The non-volatile liquid paraffin oil containing 10% stearic acid flowed over

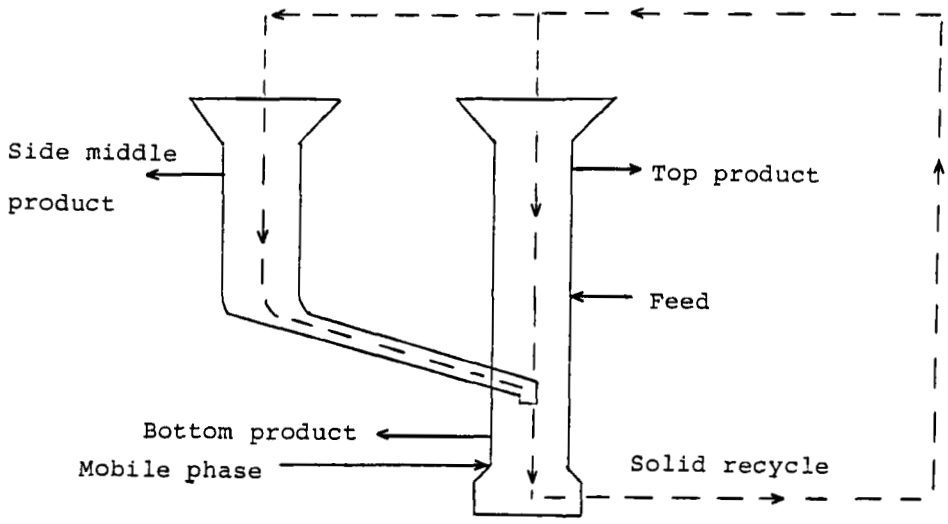


FIGURE 3
Moving bed chromatographic system for ternary separations

steel spirals counter-current to the flowing carrier gas. The ternary mixture of propionic, n-butyric and n-valeric acids was introduced into the top of the first (hottest) section, rose through section 2 and the temperature gradient was arranged so that n-valeric acid was concentrated between sections 2 and 3, n-butyric acid between 3 and 4, and propionic acid between 4 and 5. The product was withdrawn continuously and purities of 95% were obtained.

Although much work has been carried out on moving bed systems and some large-scale systems were used commercially, this type of moving bed systems have been found to suffer from the following problems:

- difficulties in achieving control of the falling solids at increased throughputs.
- mass transfer efficiency losses due to uneven packing and low packed densities
- packing attrition and packing entrainment
- relatively low mobile phase velocities necessary to prevent fluidisation.

3.1.2 Moving Column Systems

To overcome the above problems various types of equipment have been proposed which employ a circular array of parallel columns interconnected to each other. The system rotates at a controlled speed past fixed inlet and outlet ports.

Three basic schools of thought exist in the design of such systems (Figure 4); the one adopted by Pichler[40] and Glasser[41] (Figure 4a), by Luft[42] (Figure 4b), and by Barker *et al.*[43] (Figure 4c).

The main disadvantage with the first two approaches were that it was required the use of excess mobile phase, because upon entering the rotating packed column the mobile phase was divided, and the part that was passing co-currently with the column rotation was wasted. In the third approach (Figure 4c) a cam operated valve was placed between the mobile phase inlet port and the product 1 outlet

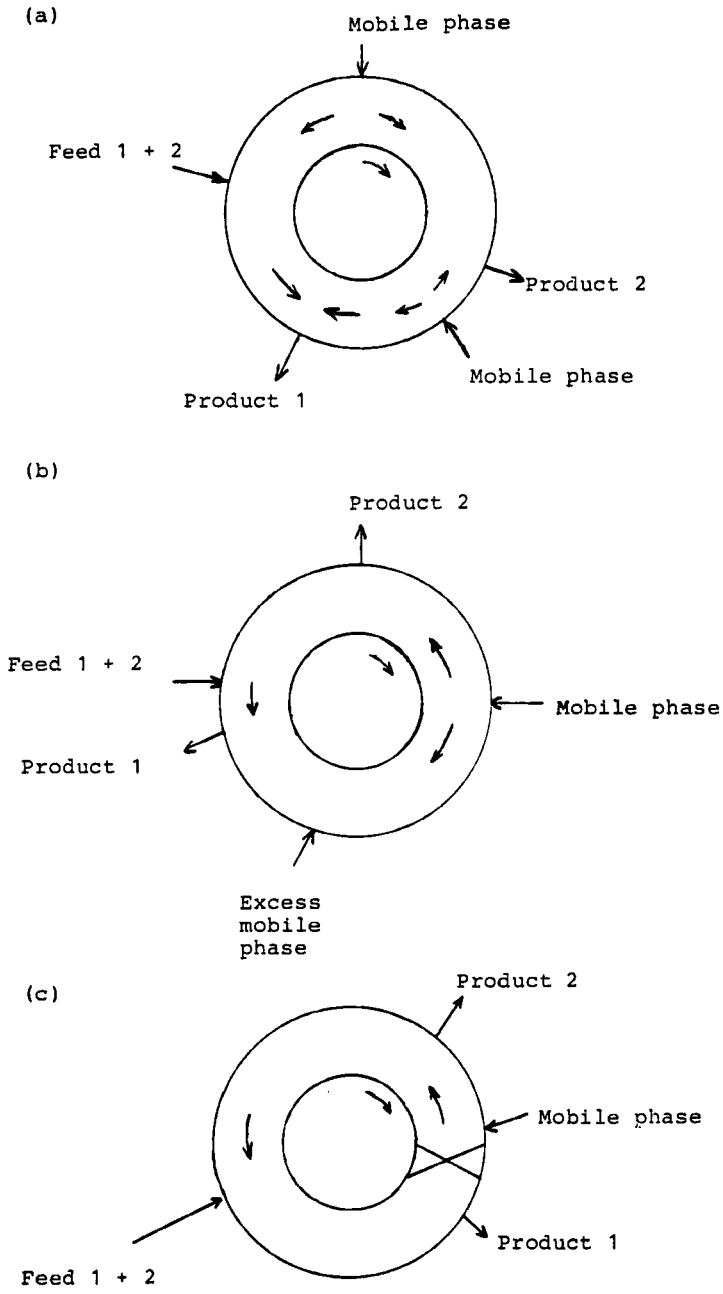


FIGURE 4
Moving column design approaches

port to overcome the above limitation to maintain the mobile phase flow in one direction. The operating principle, photographic illustrations and further details of these systems have been reported elsewhere[37,44]. The prototype equipment consisted of eight square cross-section chambers of 3.8 cm sides linked through external valves to form a circle of 1.5 m diameter. In most of the studies a 1180-850 μm C22-Sil-0-Cel firebrick packing coated with 30% w/w of polyoxyethylene 400 diricinoleate was used with air as the mobile phase[38.43].

Some of the systems examined were the separation of the azeotropic mixture cyclohexane-benzene, the close boiling system dimethoxymethane-dichloromethane, the azeotropic system diethyl ether-dichloromethane, the production of a 99% cyclohexane fraction, and the removal of five detectable impurities from a 97% pure cyclopentane fraction. In the last example using a 2.72 m long separating section over 80% of the cyclopentane was recovered as high purity product at feed rates of up to 410 $cm^3\ h^{-1}$. The same system was also used in the LC mode to separate glucose-soluble starch mixtures. The system was packed with Dowex AG-50WX2 resin in the Li^{2+} form with water as the mobile phase[45].

To increase the separating power of this equipment, Barker[46] in collaboration with the Universal Fisher Engineering Co. Ltd., Crawley, built a compact circular chromatograph made up of a cylindrical nest of forty four 2.5 cm dia x 22.8 cm long stainless steel tubes linked alternatively top and bottom to form a closed

loop. The tubes were held between two stainless steel rings, while poppet valves controlled the transfer of gas between tubes, the feed and carrier gas flow into the system and the product offtakes. The counter-current operation was obtained by rotating the whole tube bundle at speeds of 0.2 to 2.0 r.p.h in a direction opposite to the general movement of the gas phase. When a 97% pure fraction of cyclopentane was refined at 154.4 $cm^3\ h^{-1}$ almost all the cyclopentane was recovered in the product stream and no detectable impurity was present.

Other separations carried out on this equipment were the purification of a 99% cyclohexane mixture, separation of n-hexane from a crude hexane containing its isomers, separation of alpha and beta-pinenes from turpentine, separation of linalol from rosewood oil, and the separation of limonene from orange oil.

A similar system was also built by Barker and Universal Fisher Engineering Co. Ltd., to be used in the LC mode. It consisted of 44 stainless steel tubes of 0.8 cm dia and 28 cm length, held vertically between two stainless steel O rings. Barker and co-workers[45] used this equipment for the separation of glucose-starch mixtures and in the fractionation of a dextran polymer with a weight average molecular weight ($\bar{M}w$) of 96000, using Porasil D as the stationary phase. An improved version of this machine was then used extensively for dextran polymer fractionation[47].

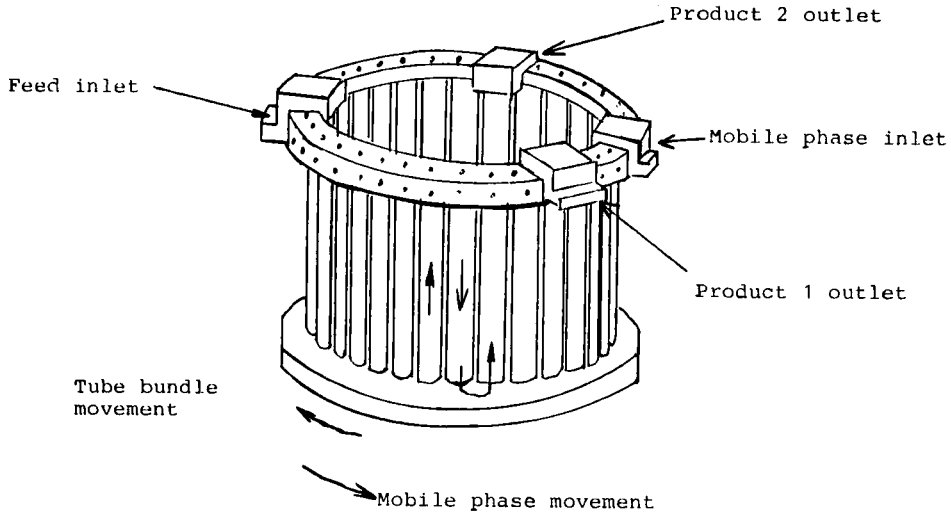


FIGURE 5
Diagrammatic representation of a circular chromatograph

A modified version of these separators were manufactured by UNIDEV Ltd., a subsidiary of Universal Fisher Engineering Co. Ltd., and marketed as a "Sequential Separator". After selling several such systems the manufacturing rights were taken over by Precision Engineering Co. Ltd., a subsidiary of Unilever.

Although a number of such systems were constructed for analytical and preparative purposes, scaling-up was difficult because there were increased difficulties in achieving a reliable mechanical seal between the static ports and the moving band of columns.

3.1.3 Simulated Moving Bed or Moving Ports Systems

All such systems employ either one column subdivided into a number of interlinked compartments or a series of static interlinked

columns, the counter-current movement being effectively achieved by sequentially moving the inlet and outlet ports in the direction of the mobile phase.

Two main approaches exist, the Universal Oil Products (USA) Sorbex technique[48-50], and the Semi-continuous-Chromatographic-Refiners (SCCR)[51,52]. In a typical Sorbex process the stationary phase, usually a molecular sieve adsorbent, is packed into a static column which has been subdivided into compartments. Each compartment is connected to a specially designed rotary master valve operating on the principle of a multiport stopcock. This carefully designed valve co-ordinates the movement of the feed and eluent inlet and two product outlet ports and thus simulates the column movement counter-currently to the liquid eluent flow, since all the Sorbex processes have operated in the liquid phase. The operating principle is shown diagrammatically in Figure 6. A pump circulates the mobile phase from the bottom to the top of the column, and the liquid rate can vary through a complete cycle depending on the needs of the liquid flow rates through the different zones in the column.

The UOP Sorbex process is usually named differently according to the application. The names used are usually, Olex for the separation of n-olefins from olefin n-parafffin mixtures, Molex for the recovery of n-paraffins from light naphthas, Parex for the separation of p-xylene from other C_8 hydrocarbons, and Sarex for

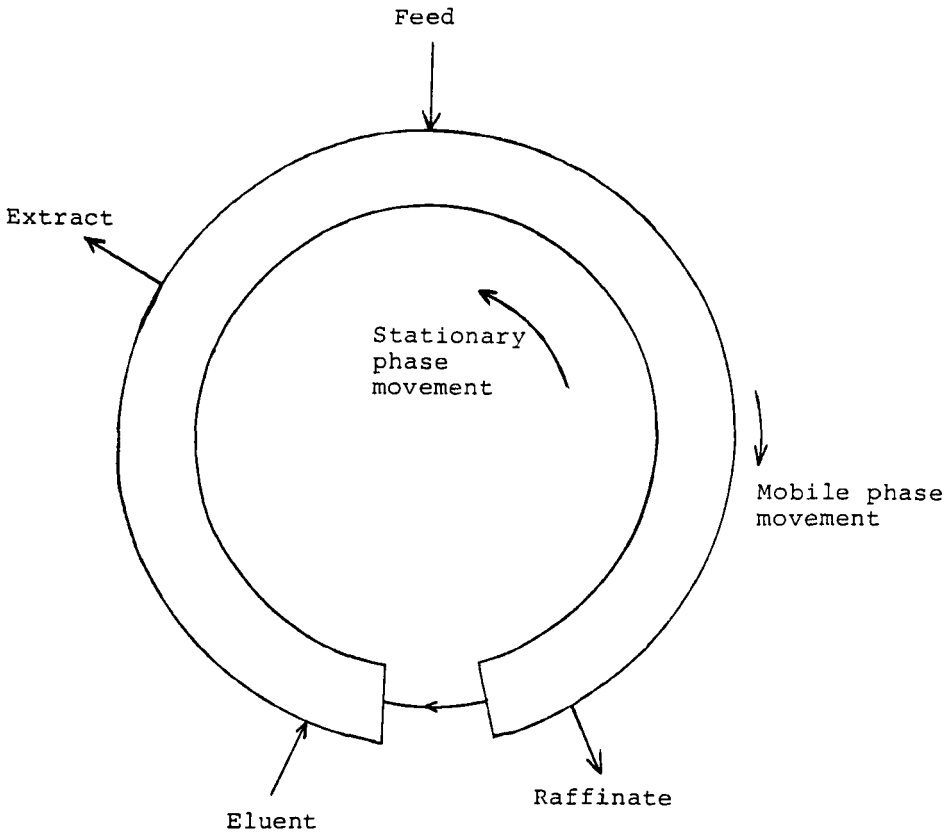


FIGURE 6
Diagrammatic representation of the UOP operating principle

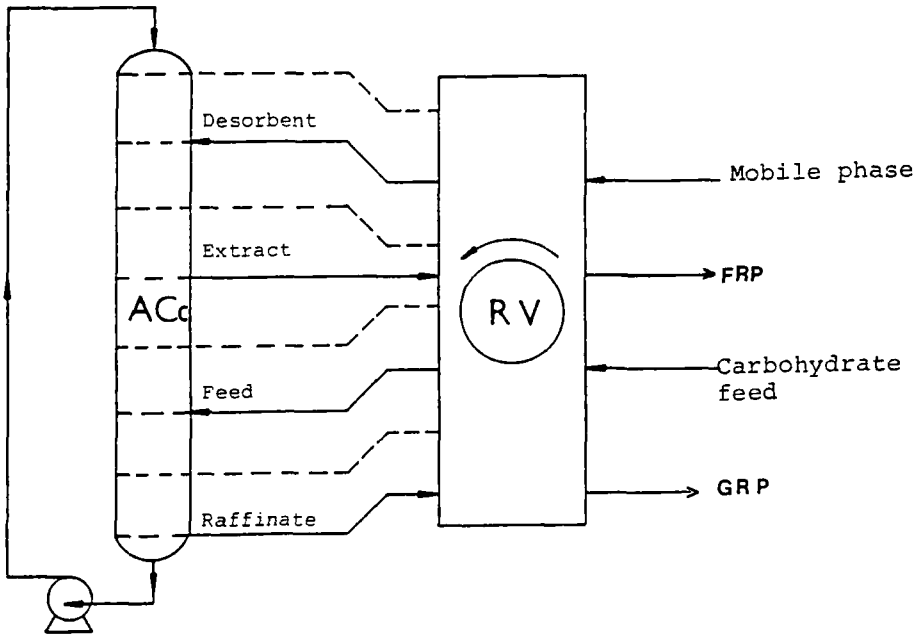
the separation of carbohydrates. Some published results for olefin separations using the Olex process showed extract purities of over 99% and extraction efficiencies of over 97%[53]. When a small-scale Sorbex plant was used for the extraction of p-cresol from a cresol mixture containing 30 to 40% p-cresol, streams containing 60-90% m-cresol and 99% pure p-cresol were obtained at

recoveries of up to 97% p-cresol using pentanol-1 as the desorbent[54].

The Sarex process has been reported[55] to be used to separate continuously a 50% w/v inverted carbohydrate syrup containing 42% fructose giving 90 to 94% pure fructose rich product streams at recoveries of over 90%. The glucose rich product was about 80% pure and both product concentrations were around 20% w/v. Unfortunately, no throughput data are available for the above separation. A diagrammatic representation of the Sarex process is shown in Figure 7.

Since 1963 over 60 Sorbex units have been licensed for eight different applications which represent an aggregate capacity in excess of 5 million tons/yr of selectively adsorbed products[53]. There are at least 20 Molex plants making n-paraffins for detergent applications and for broths in the growth of single cell protein (1976), and in 1980 22% of the world's production of p-xylene was carried out using the Parex process. In the carbohydrate field, however, the Sarex process seems to have missed the 1970's boom in high fructose corn syrup (HFCS) producing plants in the USA.

More recently (1975) Szepesy[56] built a laboratory unit working on a principle similar to the UOP Sorbex Process (Figure 6). Instead of using a "multiple compartment" vertical column like UOP, they "broke" the system down to twelve glass tubes of 300 mm length



where: FRP : fructose rich product
GRP : glucose rich product
RV : rotary valve
ACc : adsorption chromatographic column

FIGURE 7
Flowsheet of the Sarex process

and 14 mm id, connected elliptically to each other by metal fittings (Figure 3 in refs. 56 & 37). Each adjoining section was supplied with inlet and outlet ports suitably connected to a rotary valve. The feed and eluent and two product lines were connected to the valve.

The countercurrent movement was simulated by rotating the valve in the direction of fluid flow and keeping the columns stationary. The

main difference between the UOP and the Szepesey system was that the latter eliminated the need for a circulating pump and was more flexible by subdividing the UOP single column into individual columns. The Szepesy system was later modified and had the columns connected through the valve rather than to each other in order to overcome earlier problems associated with the equipment being sensitive to the pressure gradient inside. Some interesting separations were carried out on this system including the separation of C_{16} - C_{22} fatty acid methylesters.

A similar system has also been reported by Maki *et al.*[57], which is made up from a series of columns, a master valve to simulate the countercurrent operation and also a mobile phase circulation pump like the UOP. The system was used to separate glutathione (GSH) and glutamic acid (Glu), and the purity and yield of GSH in the raffinate stream were reported to be around 99%.

Hoshimoto *et al.* employed the same principle but used a rather different and more complicated mechanical configuration in their simulated moving bed adsorbers[58,59]. A schematic diagram of the separator is shown in Figure 8. Sixteen 1.38 cm id x 10.2 cm long columns were connected to a rotary valve. The valve was made up of two stainless steel disks, where the lower one was stationary and the upper was rotated counterclockwise by 22.5° at 2 to 5 min intervals, thus causing the countercurrent movement. The positions of the eluent and feed entries and the raffinate and extract outlets were fixed.

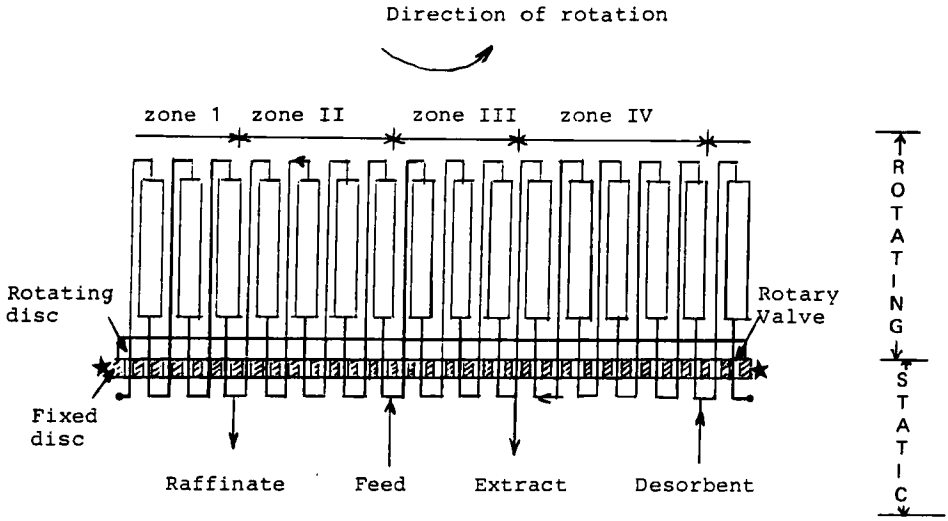


FIGURE 8
Diagrammatic representation of the Hashimoto et. al. (58) simulated moving bed adsorber

The system was packed with Y zeolite in the Ca^{2+} form, kept at 50°C, and was used to separate equimolar glucose-fructose mixtures. The system was subsequently modified by "adding" on externally to Zone 1 a number of immobilised glucose isomerase reactors to produce high fructose syrup either from fructose-glucose syrups or glucose feedstocks. The glucose was isomerised to fructose and the fructose content in the final product was around 65%. At the moment we feel that the system has still to prove itself in terms of obtaining even higher product purities, concentrations and throughputs, and that scaling-up will prove difficult due to the complexity of the rotary valve and due to problems associated with achieving perfect seals between moving flat surfaces.

Experience gained on the unreliability of large flat face moving seals under the arduous conditions demanded by the chemical industry and the awareness of the limitations associated with the various techniques mentioned above, led Barker and co-workers to develop an alternative technique to simulate the countercurrent movement of the two phases. They developed the "moving port" systems which they named semi-continuous chromatographic refiners (SCCR). The multicolumn approach was adopted to provide extra flexibility, enable easier repacking or recharging of part of the system, reduce problems with packing attrition by splitting the packing into a number of columns, minimisation of flow irrgularities, and to move "closer" to true countercurrent operation, i.e. since the simulated counter-current operation is stepwise, the greater the number of columns, the shorter the steps, and hence the nearer to true countercurrent flow. Also all moving parts were eliminated by using valves of proven commercial reliability. To each one of the stationary interconnected columns of the SCCR system six valves are attached. At the column inlet, the eluent, feed and purge valves are attached while at the outlet there are two product valves and a transfer valve, connecting through a short flow line, two adjacent columns together. Each of these valves is connected to the corresponding eluent, feed, purge and the two product distribution pipe networks. For illustration purposes a twelve column system is considered and in Figure 9 the whole system is represented as a closed loop. The feed is introduced continuously at port F, and the mobile phase flows continuously through port M. The less

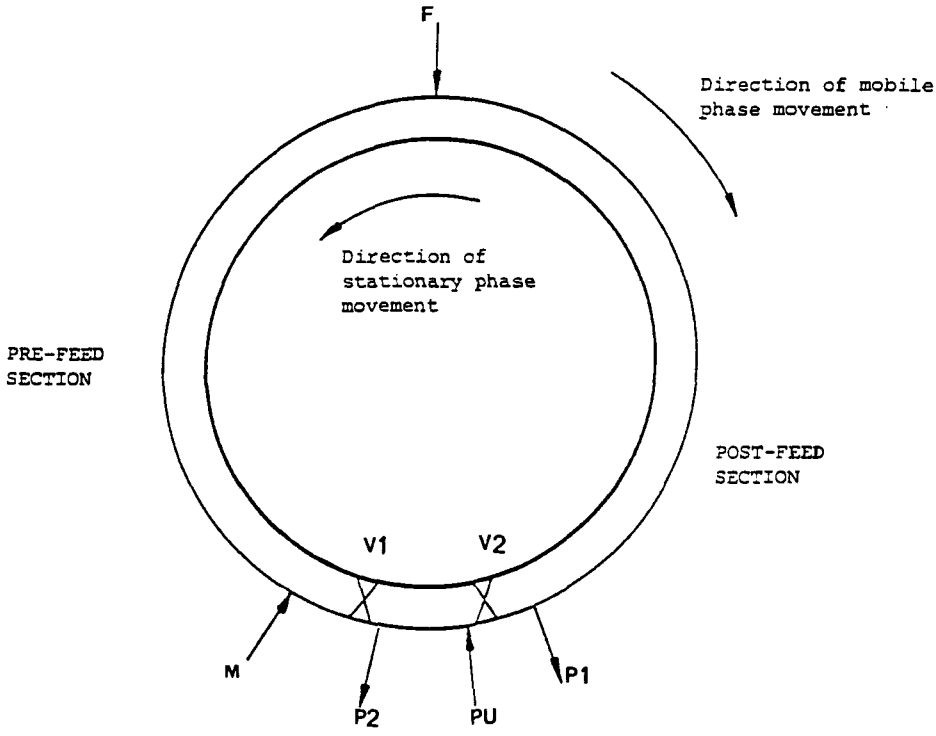


FIGURE 9
Diagrammatic representation of the semicontinuous principle of operation

strongly adsorbed component B (raffinate) moves preferentially with the mobile phase towards the product outlet P1. A section of the loop is isolated at any time by the two transfer valves V1 and V2, and an independent purge stream enters at port PU, strips the adsorbed component A and flows out of port P2.

After a predetermined time interval, referred to as "switch-time", all the valve functions advance by one position in the direction of the

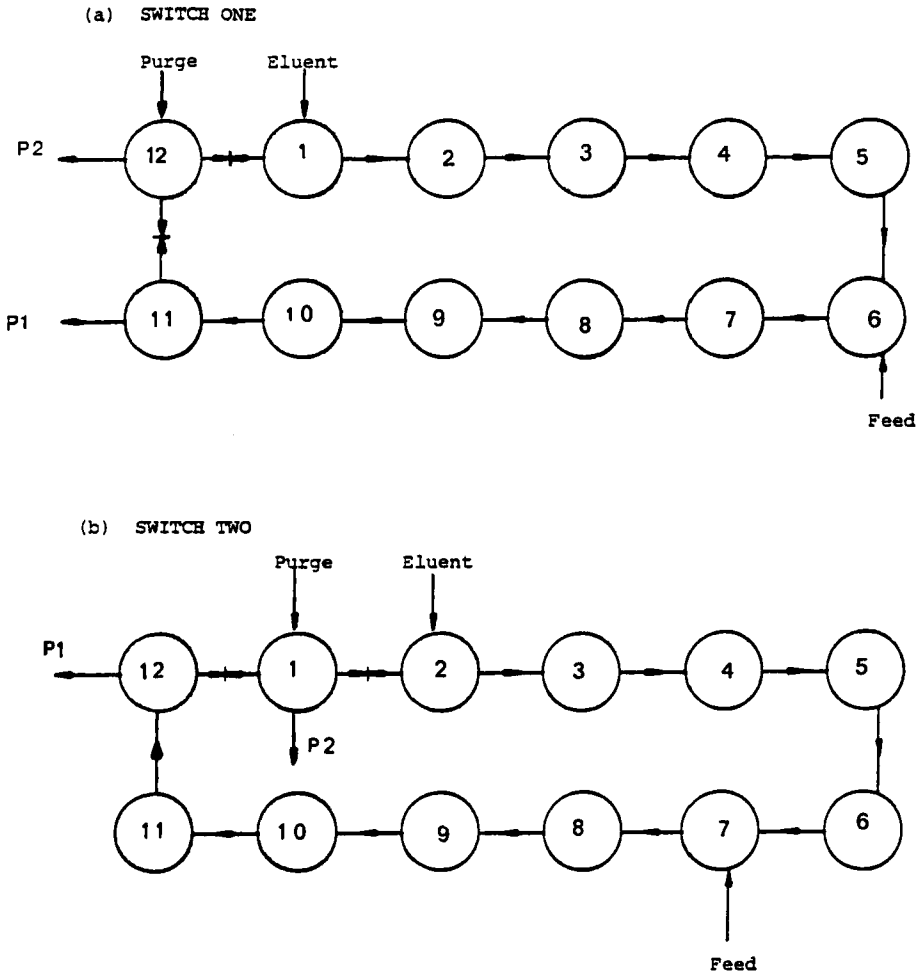


FIGURE 10
Sequential operation of the SCCR system

mobile phase flow, thus achieving the counter-current movement (Figure 10). Figure 10a represents the first switch period where column 12 is isolated and purged to give the product rich in A. Feed and eluent enter columns 6 and 1 respectively and the product rich in B is eluted from column 11. In the next switch period all

ports are advanced by one position, as shown in Figure 10b, and so on. After twelve such advancements a "cycle" is completed, and after approximately six cycles the concentration profiles in the system become reproducible and a "pseudo-equilibrium" state is reached. To achieve a separation and hence two enriched products, the rate of port advancement must be greater than the migration velocity of component A through the bed and lower than the migration velocity of B.

The theoretical analysis of the SCCR operation has been reported in detail elsewhere[60,22], while a theoretical design approach for the continuous SCCR systems from batch data can be found in references 22 and 61.

The first SCCR built by Barker and Deeble[51,52] was a gas-liquid chromatographic separator consisting of twelve 7.6 cm id x 61 cm long brass columns, and was packed with 500 - 355 μm Chromosorb P coated with 25% w/w of Silicone fluid DC 200/50. Economics dictated the use of air, as carrier, and the separation of 1,1,2-trichloro-1,2,2-trifluoroethane (Arklone P, ICI), and 1,1,1-trichloroethane (Genklene P, ICI) with a separation factor of 2.9 at 20 °C was studied initially. A wide range of operating conditions were used[51,62] with feed rates of up to 1500 $cm^3\ h^{-1}$ of equivolume Arklone/Genklene mixtures were obtained while maintaining product purities of greater than 99.5%. The system Arklone P and dichloromethane with a separation factor of 1.16 was

also studied and at feed rates of 130 cm^3h^{-1} product purities of between 92 and 99.8% were obtained.

A second such unit consisting of twelve 2.5 cm dia and 61 cm long stainless steel columns was used for fatty acid esters and essential oil separations[63]. For example, a methyl chloroacetate/ethyl lactate mixture was separated at feed rates 100 $cm^3\ h^{-1}$ and 120 °C, the product purities being over 99.9%. With some feedstocks this equipment was operated at 200°C.

The next step in the development of the SCCR machines was in line with the general trend at the time, that is, to investigate their use as liquid separators. Liquid chromatography SCCR separators of ten 5.1 cm id x 70 cm long glass columns, packed with Spherosil XOB 075 (200 - 400 μm), and operated in the size exclusion mode were used to fractionate a dextran polymer with an average molecular weight of 30000. At feed rates of 7.9 cm^3/min and feed concentration of 21% w/v the average molecular weights of the products were 95000 and 27000 for the high molecular weight (HMW) and low molecular weight (LMW) respectively.

By carefully adjusting the operating conditions the SCCR GPC fractionators were used either to remove the HMW or the LMW fractions present in the dextran macromolecular feedstock. When experiments were geared towards removing the LMW fraction of a Dextran feed with an $\bar{M}_w$ of 45000 and a number average molecular

weight, $\bar{M}_n$, of 20800 (runs A and B in Table 1), the $\bar{M}_w$ and $\bar{M}_n$ values of the HMW product streams were increased by up to 75% and 49% respectively. When the objective was changed, i.e. to reduce the M_{90} value of the LMW product below 150 000 by removing less than 15% of the dextran in the feed as the HMW product, the M_{90} and $\bar{M}_w$ values obtained were 142 200 and 49 300 respectively (run C)[64]. To overcome pressure limitations the glass columns were replaced by similar sized stainless steel columns packed with the same material[65]. The experiments were focussed on removing the HMW from the feed and producing a dextran LMW product with an $\bar{M}_w$ of less than 33000. As similar dextran feed was used in both runs shown in Table 1 (runs D and E) with $\bar{M}_w$ and $\bar{M}_n$ values of 82000 and 9000 respectively and the operating temperature kept at 60 °C. The results show first that the objectives were achieved and secondly that a reduction in the feed flow rate alters the actual "cut positions" resulting in a reduced removal of HMW dextran. The increased % dextran recoveries and $\bar{M}_w$ value give support to these findings.

The increased international need for High Fructose Corn Syrups (HFCS) as a sweetner led Barker and co-workers into examining the SCCR performance with carbohydrate feedstocks. Three different systems with column diameter of up to 10.8 cm and total length of over 7m were used to optimise the SCCR performance with feedstocks ranging from equimolar synthetic glucose-fructose to industrial low fructose syrups[22,64,66,67,68]. The ion-exchange

TABLE 1 : Dextran fractionation results obtained on an SCCR machine

RUN	Flow rates (cm^3/min) Feed	Eluent	Purge	Feed Conc. % $^{w}/_{v}$	H M W Conc. % $^{w}/_{v}$	% recovery	Product $\overline{Mw}$	$\overline{Mn}$	L M W Conc. % $^{w}/_{v}$	% recovery	Product $\overline{Mw}$	$\overline{Mn}$
A	17.5	208.8	508	23.6	1.45	78.9	78700	29700	0.09	10.3	33100	19000
B	10.7	52.1	130	21.5	3.12	86.3	73400	30900	0.16	9.4	39300	20700
C	40	101.1	413	23.1	0.94	14.1	123600	39000	1.82	82.0	49300	23700
D	60	95	300	13.4	-	-	-	-	-	76.5	29000	7500
E	40	95	300	13.1	-	-	-	-	-	83.6	29900	8100

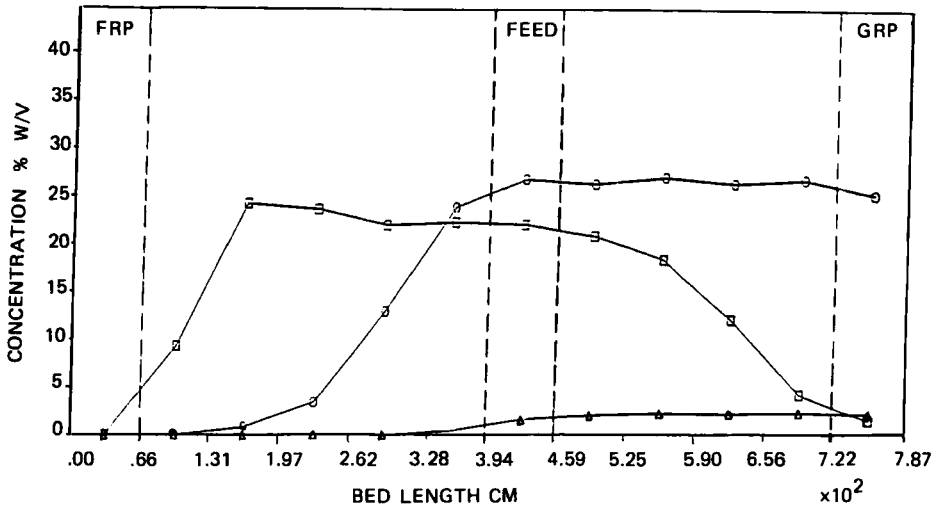


FIGURE 11
Typical concentration profile for a twelve column SCCR system.

Key:	fructose
	glucose
	maltose + oligosaccharides
FRP	fructose rich product
GRP	glucose rich product

principle was employed for the separation and a typical on-column concentration profile is shown in Figure 11. As an example of the latest achievements, when an industrial barley syrup containing 42% fructose, 52% glucose and 6% maltose and oligosaccharides was fed continuously at 66% w/v feed concentration, a throughput of 32.3 kg sugar solids/m^3 resin/h was obtained, the glucose (GRP) and fructose (FRP) rich product concentrations were 25.4% w/v and 13% w/v respectively, the FRP was over 90% pure and the GRP contained 6.69% fructose[22,60,64,69]. Alternatively, if throughput is sacrificed for better purities, product purities of over 99.9% pure

can be obtained. A computer simulation has also been developed predicting successfully the system's performance[22,69,70].

Some of the SCCR machines have also been used in a batchwise mode to compare batch and continuous separation performances[61,64,71]. Both modes were found to operate efficiently in the fractionation of macromolecules such as dextran and in the separation of different carbohydrate mixtures. For example when a ten column (10.8 cm id x 75 cm long) system was used in both batch and continuous mode for carbohydrate separations, purities of up to 99.9% were obtainable[71]. The throughput of the continuous mode however was larger and it ranged from approximately twice the batch one for synthetic glucose-fructose separations to almost five times the batch one for the separation of an industrial effluent containing dextran, glucose and fructose.

In the late 1970's Odawara *et al.* of Toray Industries Inc. (Japan)[72], patented a continuous counter-current process similar to the SCCR system, for separating fructose from glucose-fructose mixtures. The equipment consisted of eleven columns each of 2.5 cm id x 1.5 m long, packed to a height of 1.35 m with barium zeolite which complexes with fructose. The liquid stream flows through the desorption, rectification and sorption zones consisting of 5, 2 and 4 columns respectively (Figure 12). A total of 66 valves and a timer were used to simulate the continuous operation.

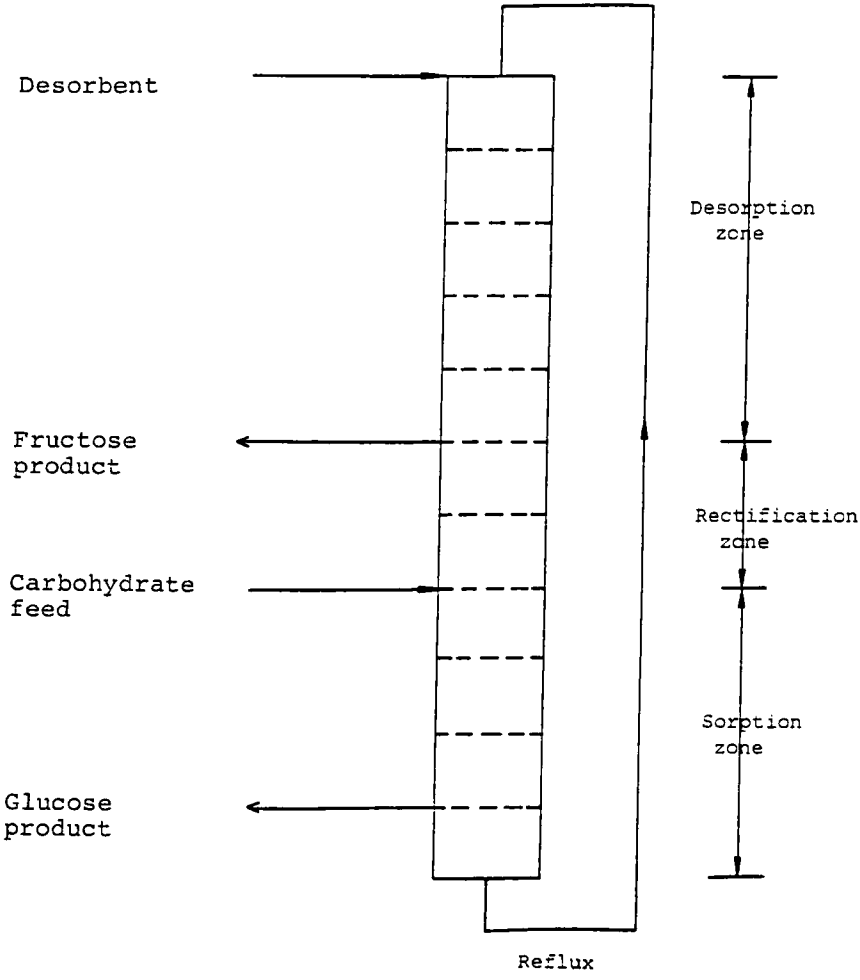


FIGURE 12
Diagrammatic representation of the Odawara process

Water was fed continuously as a desorbent at 2.9 kgh^{-1}. A 7% w/w feed containing 57.5% glucose and 42.5% fructose was introduced at 1.5 kgh^{-1} and another stream containing 1% w/w sugar solids was continuously refluxed at a rate of 8.5 kgh^{-1}. The desorption effluent was withdrawn continuously at 12.7 kgh^{-1}, had a concentration of 1% w/w and contained pure fructose. The raffinate effluent was withdrawn at a rate of 0.2 kgh^{-1}, it had a concentration of 45% w/w and contained 3% fructose. The product streams were concentrated by evaporation and the desorbent was recycled.

3.1.4 Moving Feed Point Systems

This technique is an intermediate one between conventional batch and simulated countercurrent operation.

Wankat and Oritz[73] used such a process to separate dextran 2000 from cobalt chloride in water. The system consisted of a series of fixed columns. The mobile phase was pumped continuously through the inlet into the top column the feed being introduced as a long pulse. The first feed pulse was introduced into the first column, then after a pre-determined time into the second column and so on. This continuous feed switching was controlled by a rotary valve and a timer. When the results were compared to the conventional batch system it showed that the moving feed system had up to 37% better

resolution, a peak width of up to 50% less, and double the maximum concentration.

3.2 Cross-Current Systems

In counter-current operations only two components or two different fractions can be effectively separated at any one time. The cross-current systems, theoretically at least, offer the possibility of separating simultaneously all the components from a multicomponent mixture. In crossflow systems the "stationary" phase moves perpendicularly to the direction of the mobile phase. As early as 1949 Martin[74] had suggested such a system and provided a theoretical analysis of its operation. A number of such systems have been developed and can be classified into three main categories.

3.2.1 Moving Annulus Systems

In these systems the packed annulus rotates through a fixed inlet port, while mobile phase is introduced continuously at the top of the annulus and leaves at the bottom. The components travel in helical paths around the annulus at different angles according to the relative affinities for the packing and are eluted at different points at the bottom of the annulus with the strongly retarded component travelling along the longer helical path (Figure 13). Laboratory units using a rotating annulus or a series of vertical rotating columns were first proposed by Svensson *et al.*[75,76].

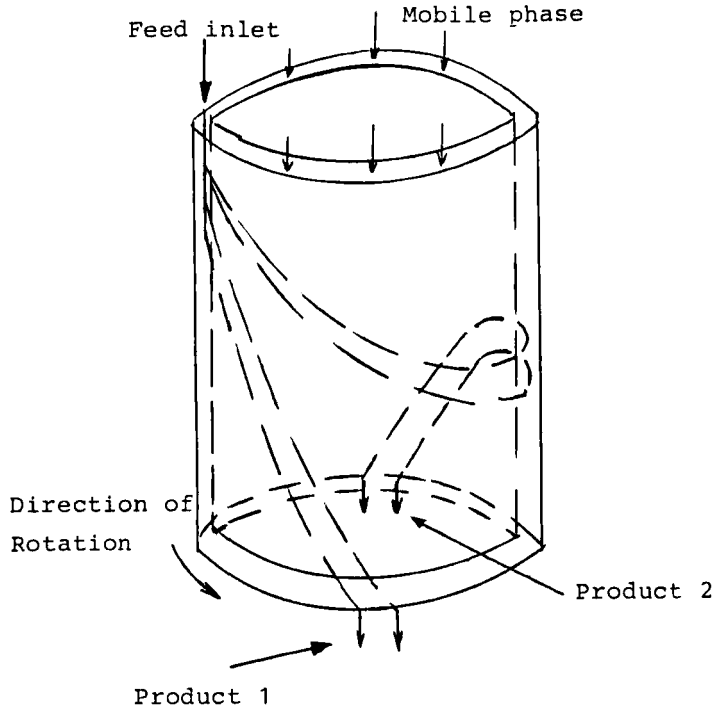


FIGURE 13
Cross-current chromatographic principle of operation

In 1969 Fox and co-workers published a series of papers[77-79] covering the design and operation of an annular gel permeation system. The column height was 30.5 cm and the inner and outlet cylinder diameters were 27.3 cm and 29.2 cm respectively, the annulus being packed with Sephadex. Feed inputs of up to 22 cm^3h^{-1} of a 5% protein concentration were partially resolved when using solvent flow rates of 1 to 15 lh^{-1} of 0.02 M Tris-HCl buffer (pH8) as eluent.

Begovitch *et al.*[80] have constructed a number of 60 cm deep annular systems having diameters of either 28 cm or 60 cm. The 28 cm diameter system was used to study the separation of copper, nickel and cobalt components from a carbonate solution. Feed rates of 6.7 cm^3 min^{-1}were employed. The system was packed with Dowex 50W - X8 cation resin (50 to 60μm) whilst 1M $(NH_4)_2CO_3$ was used as eluent with the pH adjusted to 7.8.

When an alternative solution containing 13.5% w/v zirconium and 0.41% w/v hafnium was separated using 0.9 to 1.5N sulfuric acid as eluent at 250 cm^3 min^{-1}, over 90% of the zirconium in the feed was recovered at purities exceeding 99.9% The system has also been used for Iron-Aluminium separations. Using an eluent superficial velocity of 2.29cm.min^{-1}, a rotation of 210° h^{-1} and feeding 0.4% w/v Fe and 0.7% w/v Al at 4.05 cm^3 min^{-1} 80% recoveries were obtained with product purities of over 99%.

Within the Department of Chemical Engineering and Applied Chemistry at the University of Aston, a 140 cm high x 30 cm diameter moving annulus system has been developed with either a glass or stainless steel outer annulus and with the possibility of altering the annulus thickness by up to 80% of the full diameter[81]. In the initial version the system consisted of a 297mm id borosilicate outer column and a 273mm od diameter stainless-steel inner column. The annulus was packed with a calcium charged Purolite PCR 833 resin and was used for carbohydrate separations.

As an example of its separation performance, when an equimolar synthetic glucose-fructose solution was fed at 360 cm^3min^{-1}, 90% pure glucose and fructose products were obtained at 4.8 and 2.6% w/v concentrations respectively. Although about 25% of the overlapping sugar fractions were discharged the actual throughput was over 14 kg sugars/m^3 resin/h. But since only one quarter of the bed was needed for the separation, the potential throughput using four feed points is 56 kg sugars/m^3 resin/h.

A typical on-column concentration profile is shown in figure 14. A 50% w/v concentrated solution, consisting of equal amounts of glucose-fractose and sucrose was fed at 120 cm^3h^{-1}. The eluent flow rate was 12 000cm^3 h^{-1} and the rotational speed 144 $deg.h^{-1}$.

3.2.2 Moving Column Systems

These separators consist of a circular array of parallel tubes rotating through a fixed top inlet and stationary product receivers at the "open bottom" ends. This design approach was initiated by Svensson[75,76] and Taramosso, Dinelli and co-workers[82,83,84] constructed such an equipment for the separation of volatile mixtures by gas-solid chromatography. The equipment took the form of one hundred 6 mm x 1.2 m vertical tubes arranged on a circular pitch and capable of rotating at speeds between 1 to 50 r.p.h. Knowledge of the speed of rotation of the tube bundle,

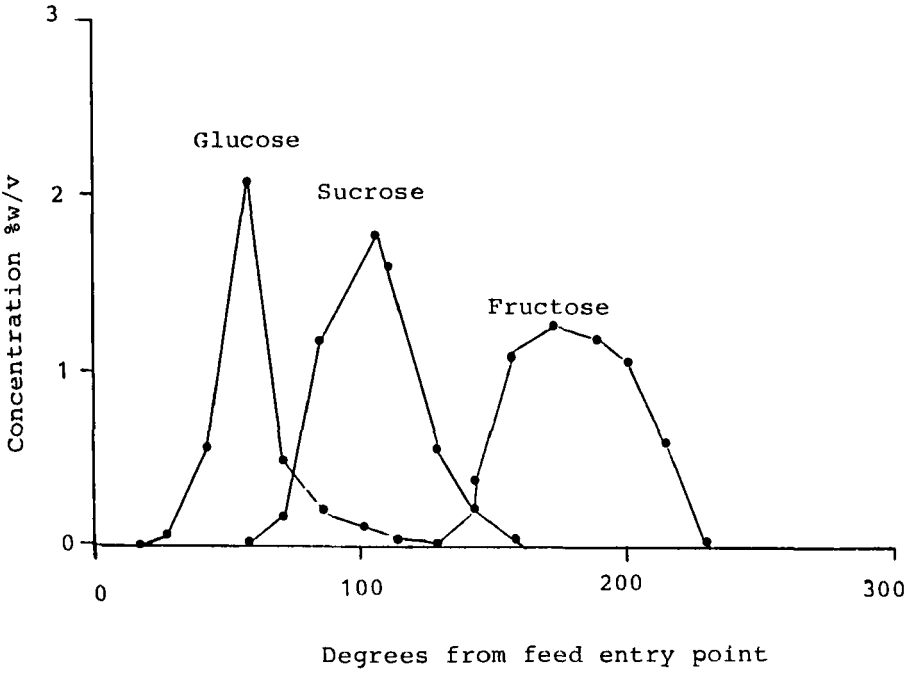


FIGURE 14
Concentration profile of an annular chromatographic system

carrier gas flow, and retention times of the components, permitted the evaluation of the distance a particular solute would travel and also from which column outlet it would be eluted. For the separation of cyclohexane-benzene mixtures on tricresyl phosphate as stationary phase, throughputs of 200 cm^3h^{-1} were achieved at product purities of 99.9%.

The use of a series of rotating columns restricts the flow continuity apparent in the moving annulus systems and in any case the same

effect could be achieved with pulsed batch columns incorporating valve switching to receive the various constituents as they leave a column. The moving annulus is the most promising one, although it is also amenable, like the moving column system, to difficulties associated with achieving a perfect seal between the ends of the rotating annulus and the stationary outlets. Although a number of small and preparative scale units exist, scaling-up may prove difficult. An alternative method of achieving the same principle is to maintain the annulus stationary, incorporate a large number of fixed outlets at the bottom of the annulus and place underneath a number of collecting vessels which will rotate at the same speed and in the same direction as the inlet feed port, (Figure 15).

3.2.3 Continuous Annular Disk Chromatographs

Mosier[85] patented equipment which used a packed annular column with radial flow of the feed and carrier gas from the inner to the outer cylinders. The packed section was rotated and the products were collected from the outer column walls. A similar system was developed by Moskvin[86] with the exception that the packing was held between two rotating disks.

Sussman and co-workers[87,88] have reduced these radial flow chromatographs to essentially radial thin layer chromatographs by using no packing but solvent coated rotating disks[87] spaced 50 - 150 μm apart. Disc diameters of up to 60.8 cm have been used and

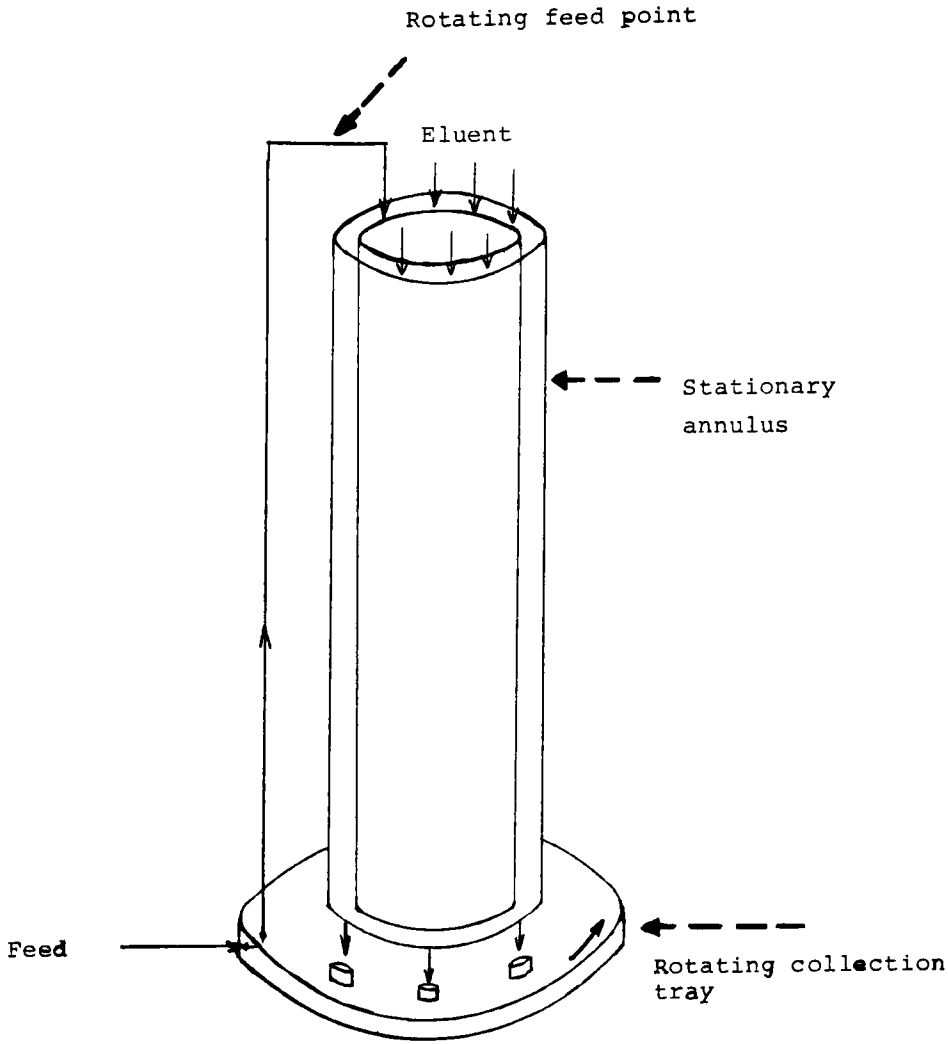


FIGURE 15
Alternative way of achieving cross-current operation

to enhance the uniformity of the chromatographic channel, plastic spacers hold the discs apart to form channels about 0.01 mm wide. These systems can be used for multi-component separations and have considerable value for small-scale applications.

Scaling-up is thought to be difficult but a possible approach is by using a "multistack" type of system.

3.3 Co-Current Flow Systems

In principle batch chromatography falls under this category. However, over the last twenty years there has been considerable interest in cyclic separation processes, with additional operating complications, which permit continuous or semi-continuous feed to various types of chromatographic separators and which can be considered as an extension to batch chromatography. Thompson[89,90] developed a sinusoidal flow system using a single analytical column in which the inlet stream varied from 100% carrier gas to 100% feed mixture, so that the concentrations of all the components in the feed mixture oscillated sinusoidally. As the concentration waves travelled through the column they were differentially retarded and attenuated by the stationary phase. By adjusting the frequency and flow rate, component waves emerge from the column out of phase with one another so that by a suitable valve switching procedure and the use of a product collector, the various components can be collected separately. With a 50:50 ethane-propane mixture and benzyl ether as the stationary phase and

CO_2 as the carrier gas products 70% pure in ethane and 74% pure in propane were achieved at a total feed rate of 82 cm^3 min^{-1} and a frequency of 40 c.p.m. The process of parametric pumping was demonstrated by Wilhelm *et al.*[91,92] who used mobile phase flow and column temperature cycling within a solid adsorption bed. Mobile phase flow was alternated up and down the column, the packing being heated during the downward flow to utilise the temperature dependence of the partition coefficients. Kuhn *et al.*[93] have used the temperature dependence of the partition coefficients in flowing liquid columns for the separation of multi-component mixures. Since the liquid was flowing counter-currently to the carrier gas stream this type of system was judged to be a moving bed countercurrent system.

The idea of passing a thermodynamic wave such as temperature through a packed bed was utilised by Zhukhovitskii[94] in 1960 who used a rotating heater to develop temperature waves in a gas chromatography column to produce continuous multi-component separations. In cyclic zone adsorption, fluids to be separated are pumped in one direction through a series of columns. Separations have been performed either by heating and cooling the columns, or the entering stream periodically[95]. This technique has been studied and developed further by Pigford *et al.*[96].

The periodic variation of a thermodynamic variable has not been confined to temperature. Busbice and Wankat[97] studied the partial

separation of glucose-fructose mixtures using a travelling pH wave in a cycling zone adsorption system. Before these cyclic co-current flow processes are scaled up to commercial sizes, considerable development work is required.

Another mode of operation is electrochromatography[98,99] which combines adsorption chromatography and electrophoresis and operates with continuous feed introduction and product collection. The process uses the different extents of adsorption of the components for the stationary phase and differences in the electrophoretic mobilities to achieve separation. The commerical large-scale exploitation of such systems has yet to materialise.

Although this chapter carries out a wide review of the various batch and continuous systems available, because of the great separating potential of chromatography one recognises the continuous development of new systems and modifications to existing systems. In this work, specific emphasis has been paid to systems that are judged to offer the greatest commercial potential.

4.0 CHROMATOGRAPHIC REACTORS AND REACTOR-SEPARATORS

The separation capabilities of the chromatographic systems and their potential as chemical reactors and combined reactor-separators has been recognised world-wide over the last twenty five years.

Although increasing interest is shown in the application of chromatographic systems as reactor-separators, their employment for large-scale operations has not yet materialised. An increasing amount of work has been carried out on the modelling of such systems to provide a better understanding of their operation. During operation the stationary phase in the system can either act as a catalyst and as an adsorbent, or it can act only as adsorbent with the reaction carrried out in the mobile phase. The combined operation of reactor-separators has the potential to reduce process costs (operating and capital) and higher conversions are possible by shifting the equilibrium in reversible reactions. A selection of such applications are summarised here.

Since the early sixties, Roginskii *et al.*[100,101] in the USSR, and Magee *et al.*[102,103] in the USA reported the employment of chromatographic reactor separators and produced a theoretical basis to describe their operation. A comprehensive review has been carried out by Villermaux *et al.*[104,105]. Langer *et al.*[106,107] employed a liquid chromatographic reactor to obtain kinetic rate constants. Mile *et al.*[108] studied the catalytic dehydration of cyclohexane to benzene in a gas chromatographic reactor and reported an enhancement of product yield above equilibrium, verifying the equilibrium displacement. Unger and Rinker[109] carried out the exothermic ammonia synthesis beyond equilibrium limitations by pulsing nitrogen, with hydrogen as the carrier, through a packed bed of catalyst and adsorbant. Three columns

were used of 0.63cm diameter and 95 cm length packed with a mixed bed consisting of 50% catalyst and 50% adsorbent. They suggested that it might prove economical in industry to use the pulsed chromatographic reactor as a first stage in series with a conventional NH_3 synthesis reactor.

Takeuchi and co-workers[110,111] studied the catalytic oxidation of CO on a 1.4 cm id x 55 cm long moving bed chromatographic reactor, and demonstrated successfully that reaction and separation were actually taking place simultaneously. Aris *et al.*[112,113] used a similar system to model the hydrogenation of mesitylene with excess hydrogen over a Pt on alumina catalyst. The system used was 1.27 cm dia x 17.8 cm long. Aris, Carr and Cho[114,115] modelled the acid catalysed hydrolysis of methylformate in a continuous flow annular chromatographic reactor with a rotating feed point. The equipment was packed with activated charcoal and consisted of two concentric cylinders, an outer of 20 cm od and an inner of 17.8 cm od. The total length was 40.6 cm.

Hashimoto *et al.*[59] used a continuous countercurrent system, for the production of higher-fructose syrup (45 to 65% fructose), involving selective adsorption of fructose and an immobilised glucose isomerase reaction. The continuous countercurrent contact of the liquid streams with the solid adsorbent was simulated by advancing adsorption columns against the fixed inlets and outlets of liquid streams without actual movement of the solid adsorbent,

while the immobilised enzyme reactors were stationary (also see Section 3.5). A total of 16 adsorption columns were used packed with Y zeolite (Ca^{2+} form). Each column was 1.38 cm dia x 10.2 cm long. Seven reactors containing the immobilised glucose isomerase were connected to the system, and were of 1.38 cm dia x 18 cm length. Although fructose purities of up to 65% were obtained the research groups prime objective was to model the operation.

The first successful production of useful substances by bioreactor using an immobilised biocatalyst was the continuous production of L-methionine by asymmetric hydrolysis of acetyl-DL-methionine using immobilised amino acylase, which was industrialised by Tanabe Seiyaku in 1969[116].

High fructose corn syrup (HFCS) is an example of a large scale commercial production utilising immobilised biocatalysts. The commercial success is attributed to two factors - the development of highly active and stable glucose-isomerase and the progress of immobilised technology. The list of companies employing or associated with the development of glucose-isomerase systems includes Clinton (US pat: 3788945), Corning (US pat: 3992329), Novo (Brit pat: 1362365) and ICI (US pat: 3645848, 3935068).

Over the last three years Barker and co-workers[22,117-120] have studied an alternative way of synthesising the macromolecule dextran using batch chromatographic biochemical reactor-separators.

The systems were packed with Ca^{2+} charged resin and sucrose was converted to dextran and fructose in the presence of the enzyme dextransucrase which was added to the eluent stream flowing through the chromatographic bed. At the same time the reaction products were separated simultaneously, ie the fructose was retarded immediately as it was produced by complexing with the calcium ions on the resin, the dextran formed was size excluded and migrated with the mobile phase. The substrate sucrose was migrated at an intermediate rate and was gradually converted to fructose and dextran. The principle is illustrated in figure 16 where three different stages are considered; ie the sucrose injection, an intermediate interval, final peak positions and product elution. Based on the literature it is believed that this is the first time flowing enzyme streams have been used for biochemical reactor separator operations.

By employing chromatographic bioreaction-separation the need for additional separation steps is minimised, whilst the acceptor fructose is removed from the reactor mixture immediately as it is formed resulting in the production of more high molecular weight dextran.With this method of processing it is also possible to obtain pure fructose as a useful byproduct.

This novel dextran biosynthesis has been carried out successfully on glass batch columns 1 cm id x 200 cm long and also 2 cm id x 175 cm long where high sucrose conversions have been achieved. A

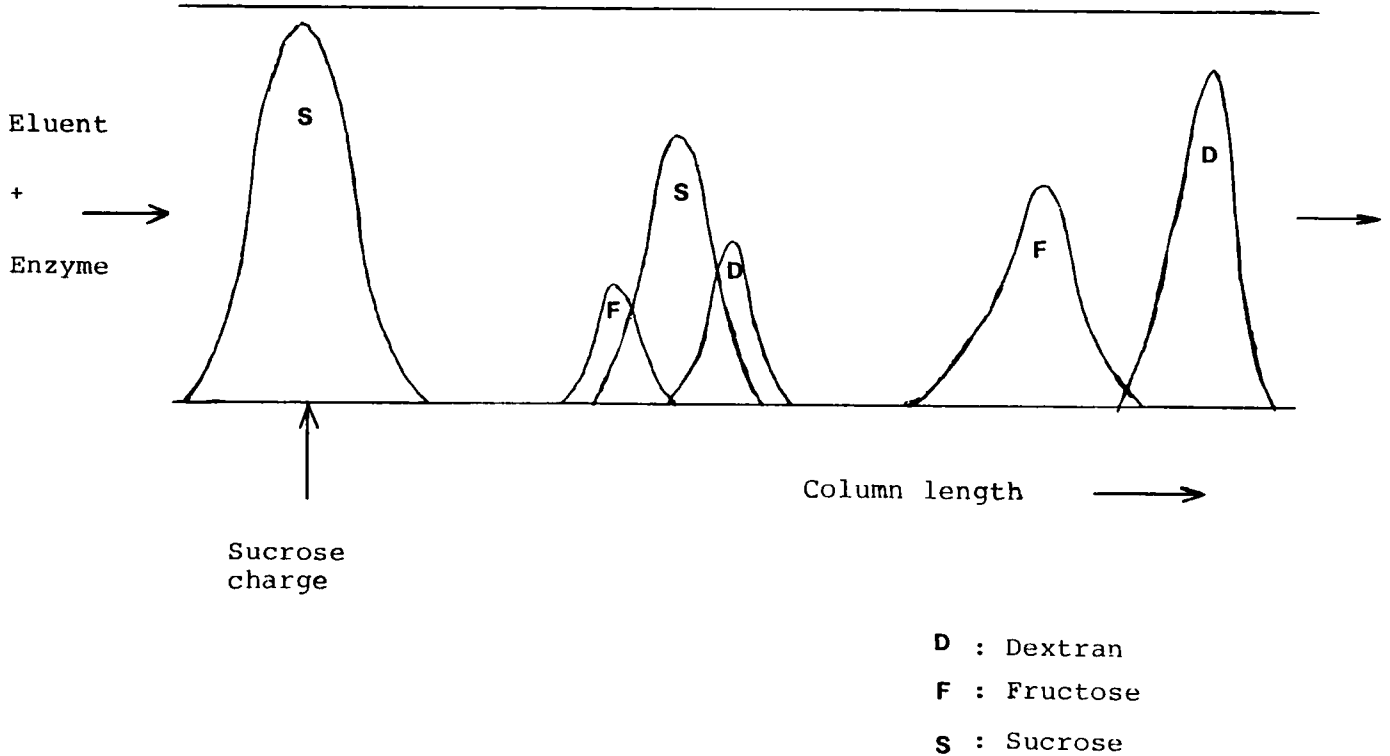


FIGURE 16
Principle of batch chromatographic bioreaction-separation

comparison of the dextran produced by the conventional batch reactor with the new batch chromatographic bioreactor-separator showed that at high feed concentrations, of over 15% w/v sucrose, the dextran produced had over 79% more high molecular weight (>157000) present. The process has been scaled up further to 5.4 id glass and stainless-steel batch columns with lengths varying from 30 to 230 cm; sucrose conversions of over 80% have been achieved at 4 hour sucrose residence times.

5.0 CONCLUSIONS

The separating power of chromatography has been recognised widely and although chromatographic processes of various configurations are used increasingly, some chemical companies appear to be reluctant in adopting them even though their viability and success has been demonstrated in the States and part of Europe. The successful operation of chromatographic systems as chemical and biochemical reactor-separators has opened new horizons, and the fields of application will be expanded further with the development of new chromatographic media of improved separating and enzymatic and catalytic properties. For the immediate future one can foresee increasing use of the chromatographic bioreaction-separation principle in the biotechnology field.

Large-scale batch chromatography has been widely used for carbohydrate separations and as it has been shown above that batch

and continuous processes are also employed in hydrocarbon, biochemical and other separations. Choosing however, the appropriate chromatographic mode of operation is not easy. Experimental results[61,64] have indicated that at high feed concentrations of binary mixtures the batch operation is slightly better in terms of product quality, while the continuous operation offers better throughputs, is more flexible, requires no recycling, allows continuous unattended operation and ensures constant product quality.

Although these advantages appear to favour the continuous mode, there are cases where the batch mode is superior and the selection of the most appropriate mode of operation for any given mixture separation needs careful consideration. Further development is needed with moving annulus systems but their ability to separate multicomponent mixtures will make the effort worthwhile.

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