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CONTINUOUS SEPARATION OF CARBOHYDRATES BY ION-EXCHANGE CHROMATOGRAPHY

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ABSTRACT

A synthetic mixture of fructose, mannitol and sorbitol was continuously separated by a chromatographic method using a cation-exchange resin (Dowex 50W-X8) in its Ca^{2+}-form as the stationary phase. An annular chromatograph (AC) was used to achieve a continuous mode of operation. Distribution and mass transfer coefficients of the three substances as well as bed properties were obtained by batch chromatography. The separation was simulated mathematically in terms of an approximate linear chromatographic theory was applied to the modeling of the behavior of the continuous separations. The influence of rotation rate, column loading, eluent flow rate and feed concentration on the resolution of the individual peaks were investigated.

INTRODUCTION

For some time there has been a trend toward the increasing use of liquid chromatography in industrial processes. The recovery of glucose and fructose from a high fructose-corn syrup by ion-exchange chromatography is an important high-throughput example in the food-processing industry. Many purification steps in the production of pharmaceutics involve chromatography. A potentially important application for the pharmaceutical

industry as well as other areas is the separation of fructose, mannitol and sorbitol. Mannitol and sorbitol are commonly produced by catalytic hydration of fructose. Both sugar alcohols are used in numerous fields including foods, pharmaceuticals, cosmetics, textiles and polymers.

Using ion-exchangers in their calcium form is a well known and widely used procedure for the chromatographic separation of carbohydrates (1). Separation of sugars with calcium-exchanged, strong-acid-type, cation exchange resins is mainly based on a ligand-exchange between the water molecules held in the hydration sphere of calcium ions and one or more hydroxyl groups of a polyol (2).

Chromatography in its conventional implementation is a batch process which allows the separation of multicomponent mixtures into individual species. In the simplest case a small quantity of the mixture to be separated is introduced onto the top of a packed column. The various components are resolved by their selective retardation as they are transported through the adsorptive phase by a moving fluid (eluent). Chromatography with its high resolution capabilities and near universal applicability, lacks only throughput capacity and the fact that the streams are diluted when they are recovered to make it the ultimate separation technique.

Many attempts have been made to increase the capacities of chromatographic devices either through repetitive or cyclic operation on large diameter fixed-bed columns, or through continuous feeding and removal of mixtures and their components in moving-bed systems (3). This work is focused on a rotating annular chromatograph which is a cross-flow system where the chromatographic bed moves perpendicularly to the direction of fluid motion within the bed. The AC in its present form was developed at the Oak Ridge National Laboratory. The concept has been successfully applied to a number of separations of potential commercial interest, including the separation of metals (4-7), the separation of sugars (8,9), the separation of amino acids (10) and recently the separation of proteins (11).

The apparatus consists of an annular bed adsorbent particles, packed between the space of two concentric cylinders. The column assembly is slowly rotated about its axis and the annular bed is uniformly supplied with eluent. The feed to be separated is introduced in only one sector of the circumference at a position which remains stationary in space. The rotation of the sorbent bed causes the separated components to appear as

helical bands, each of which has a characteristic stationary exit point. This exit point of each compound is dependent on three factors: a.) linear flow velocity of the eluent; b.) the distribution coefficient of the species between the stationary and the fluid phase under given conditions; c.) rotation rate of the annulus. As long as conditions remain constant, the retention time of each component and thus the angular displacement from the fixed feed entry will also remain constant. Hence the separation process is truly continuous.

EXPERIMENTAL

Fixed Bed Apparatus

Equilibrium and mass-transfer parameters were determined by chromatographic experiments in a conventional low pressure liquid chromatography system by injecting a defined volume of the pure sugar solution onto the column. The main part of the apparatus was a 40cm long × 1.6cm i.d. glass column (Pharmacia) filled with a Dowex 50W-X8 resin. The column was equipped with a Rheodyne Teflon six port valve and a 1ml sample loop. Eluent was supplied by a Perkin Elmer HPLC pump (model 250). Piping and fittings were all made from PVDF. The effluent of the column was continuously monitored with a refractive index detector (Waters model 401). Blue Dextran, a high molecular weight carbohydrate (MW = 2×10^6) was used to determine the bed void fraction.

AC Apparatus

A schematic of the apparatus used for the continuous separation is shown in Figure 1. The AC unit was constructed by IsoPro International (Oak Ridge, TN.) of Plexiglas, PVC and stainless steel and is similar to the unit described by Bloomingburg (12). For the size and operating specifications of the AC see Table 1. The annular bed is located between two concentric cylinders. The outer cylinder is closed at the top by a PVC flange. The cylinder itself is made of clear Plexiglas to allow visual observation during the experiments. The inner cylinder is constructed of solid PVC and is shorter then the

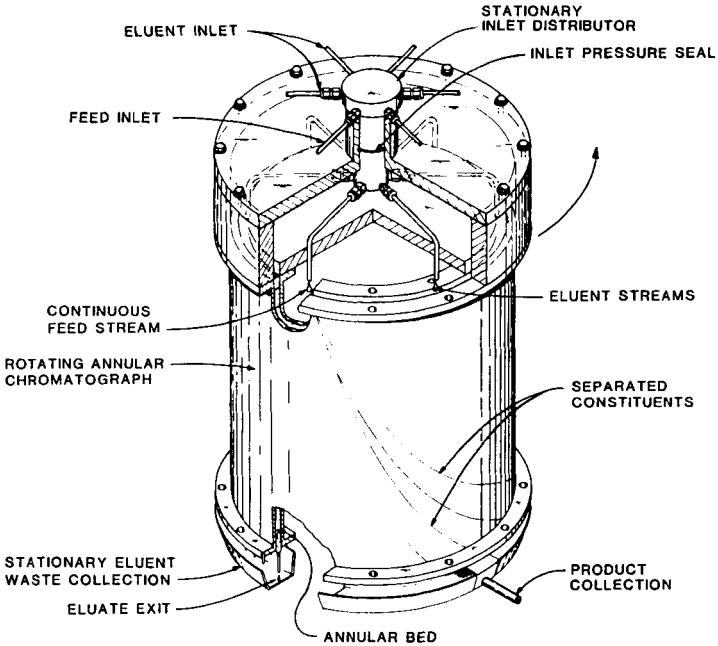

Figure 1. Conceptual view of continuous annular chromatography.

TABLE 1: CHARACTERISTICS OF THE AC

Outer Cylinder I. D.	12,7 cm
Inner Cylinder O. D.	11,4 cm
Annulus	0,65 cm
Cross-Sectional Area	24,6 cm^2
Pressure Limit	3 bar
Bed Length	31 cm

outer one leaving a head space at the top which allows the eluent to distribute evenly over the entire annulus. A stationary stainless steel header with two Teflon O-ring seals is inserted through the top flange for the introduction of the feed and the eluent streams. At the bottom of the unit the two cylinders are attached to a second PVC flange. This flange contains 90 1/8 inch exit holes, each fitted with a porous polyethylene plug and a short section of stainless steel tubing. The exit holes are evenly distributed at 4^{o} intervals along the annulus. To sample the product as a function of angular position, flexible, capillary tubing is attached to one of the chromatograph's exit tubes and to the inlet of differential refractometer (Waters model 401). By observing the concentration as a function of time a chromatogram of the whole circumference could be obtained. A digital speed drive system with feed back control and the appropriate gear reducers allows the AC to be rotated over a wide range of rates (10 - 600^{0}/h).

The resin (Dowex 50W-X8) was slurry packed in the annular unit. A 5cm-deep layer of glass beads (0.1cm in diameter) was packed on top of the resin. To assure that the resin in the column ultimately achieved the desired final chemical form, it was first converted to the H^{+}-form by pumping through 3N HCl, then converted to the Ca^{2+}-form using 2N $CaCl_2$-solution. After the column was purged of excess Ca^{2+} the annular bed settled to a depth of 31cm.

The eluent, deionized water, was introduced into the column by a Milton Roy (LMI) positive displacement pump. To reduce pulsation a pulse dampener was inserted between the pump and the column. Feed was delivered to the stationary inlet port by an Alltech HPLC pump (model 325). The tip of the stationary steel nozzle was located within the glass bead layer. As the AC unit rotates, the glass beads (0.1 cm in diameter) flow around the feed nozzle without significantly disturbing the resin bed below and preventing convective mixing of feed and eluent in the head space of the AC.

The carbohydrates used in the study were of analytical grade D-fructose, mannitol and sorbitol purchased from Fluka and not further purified. Typical concentrations during the experiments ranged from 10 to 100g/l. Blue Dextran (Fluka) in a concentration of 0.5g/l was used as a tracer with its peak maximum representing t_0. Dowex 50W-X8, a strong cation exchange resin, (Dow Chemicals) used as the stationary phase was specially screened to a particle size between 38 and 45 microns when wet.

THEORY

The modeling of an AC has been extensively investigated and since it has been extensively reported (13-15), we shall only outline the part used in the current studies. It has been shown that the one-dimensional continuity equation is analogous to the two-dimensional by making the following change of variable:

$$\theta = \omega * t \qquad [1]$$

As described elsewhere (15) the AC continuity equation neglecting axial dispersion is:

$$\omega * \varepsilon * \frac{\partial c}{\partial \theta} + \omega * (1-\varepsilon) * \frac{\partial q}{\partial \theta} + u * \frac{\partial c}{\partial z} = 0 \qquad [2]$$

Using a film model, as proposed by Howard (8) the fluid particle mass transfer may be written as:

$$\omega * (1-\varepsilon) * \frac{\partial q}{\partial \theta} = k_0 * a * (c - c^{\times}) \qquad [3]$$

Since the uptake of sugars by ligand exchange exhibit a linear dependence on their concentration in the liquid phase up to 100g/l (8) the concentration of the solid phase and the liquid phase can be related by a linear distribution coefficient, K.

$$q = K * c^{\times} \qquad [4]$$

Carta (16) has developed an exact analytical solution for the general case of finite-width, periodic-feed applications while retaining the assumption of linear equilibrium and negligible axial dispersion. Carta's solution, originally describing the behavior of a fixed bed, can be transformed with the use of equation [1] to give the solution applicable to geometry and operation of the AC. That results in equation [5]:

$$\frac{c(z,\theta)}{c_F} = \frac{\theta_F}{\theta_F + \theta_E} + \frac{2}{\pi} \sum_{j=1}^{\infty} \left\{ \begin{array}{l} \frac{1}{j} \exp\left[-\frac{j^2 k_0 * a * z}{j^2 + r^2 * u} \right] * \sin\left[\frac{j\pi\theta_F}{\theta_F + \theta_E} \right] * \\ * \cos\left[-\frac{j\pi\theta_F}{\theta_F + \theta_E} + \frac{2j\pi\theta}{\theta_F + \theta_E} - \frac{2j\pi z \omega \varepsilon}{u * \theta_F + \theta_E} - \frac{j r k_0 * a * z}{u * j^2 + r^2} \right] \end{array} \right\} \qquad [5]$$

with:

$$r = \frac{k_0 * a * (\theta_F + \theta_E)}{2\pi * (1-\varepsilon) * K * \omega} \qquad [6]$$

Assuming no interactions between species, a condition of the linear assumptions, Equation [5] can then be applied to each component in the feed mixture independently to compute concentration profiles for the individual components. A simple computer program has been written to handle the series computations leading to the concentration profiles.

RESULTS AND DISCUSSION

The distribution and mass-transfer parameters for the three carbohydrates determined as mean values are listed in Table 2. Feed concentrations were typically 10g/l. The values are estimated from pulse injections of the individual carbohydrate onto the stationary column. The retention time of each component was used to calculate K, the distribution coefficient, and the mass transfer coefficient, *koa*, was computed using the distribution coefficient and the width of the peak using the standard method for linear chromatograms described by Howard et al. (17). Injecting blue dextran into the column, and observing its retention time, allowed computation of the bed void fraction, ε. It was found to be 0.33, which is normal for closely-packed spheres with a narrow size range. The calculated values quoted in Table 2 were subsequently used for the theoretical prediction of the continuous experiments, based on the Carta solution (16).

The Annular Chromatograph experiments were performed under the conditions shown in Table 3. The influence of the rotation rate, feed flow- and eluent flow-rate on the resolution of the peaks were studied by varying each parameter in turn. Resolution, R, is defined as

$$R = \frac{2\,\theta_2 - \theta_1}{W_1 + W_2} \qquad [7]$$

where $_1$ and $_2$ are the angular displacements (from the feed point) of the maximum concentrations of constituents 1 and 2, and W is the constituent bandwidth. Measurements were made at least 2-3 hours after start to ensure steady state conditions, although it is likely that steady conditions prevailed almost from the beginning of the experiments.

Figure 2 shows the comparison of experimental AC results and calculated ones using equation [5]. It is obvious that the agreement between theory and experiment is

TABLE 2: DISTRIBUTION AND TRANSPORT PARAMETERS

Species	Distribution Coefficient	Mass-Transfer Coefficient
Fructose	0.6	0.036
Mannitol	0.93	0.074
Sorbitol	1.5	0.08

TABLE 3: BASE CONDITIONS FOR THE AC EXPERIMENTS

Rotation rate	180°/h
Eluent flow-rate	15.5 ml/in
Feed flow-rate	0.5 ml/in
Feed Concentration	50g/l fructose 50g/l mannitol 50g/l sorbitol

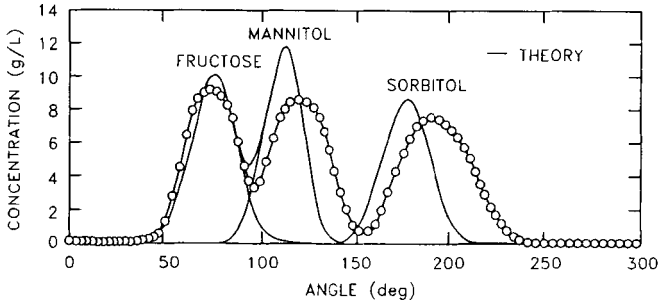

Figure 2. Construction details of CAC apparatus.

excellent for fructose. Elution of mannitol and sorbitol occurs slightly later then estimated by the model. The experiments were conducted at much higher concentration in the AC than in the batch column, the packing may well have been slightly different, and the possibility competitive isotherms in the multicomponent feed mixture may have contributed to the difference. It has previously been shown by DeCarli et al. (9) that neglecting dispersion may lead to this effect, since dispersion tends to be more manifest at higher retention times. The tailing of the sorbitol peak which cannot be found in the

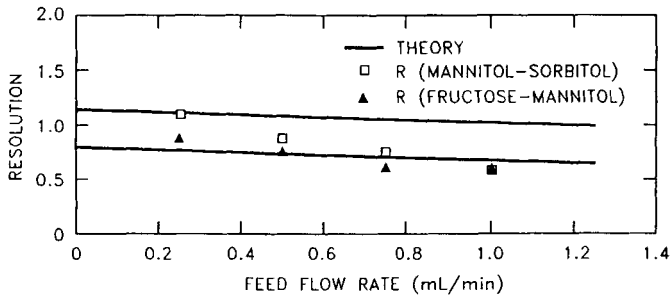

Figure 3. Comparison of dispersion in a fixed bed and a CAC unit using resins with diameters of 45 and 380 μm. $Pe = 2vR_p/D_e$, $Re = 2uR_p/\nu$

theoretical prediction represents the difference between a linear and a nonlinear isotherm, which may be another indication changes caused by higher feed concentration

The effect of rotation rate was studied in a series of experiments at the basic conditions listed in Table 3 while varying the rotation rate between 90 and 250°/h. Figure 3 shows the effect of the rotation rate on the resolution. As expected the resolution decreases with decreasing the rotation rate. A good agreement between the theory and the experimental values is obtained. This result is similar to that found by Begovich et al. (14).

The effect of the feed-flow rate on the elution position of the individual species was investigated. The feed flow was varied between 0.25 and 1.0 ml/min. Figure 4 shows that the elution position does not depend on the feed flow rate, which is in excellent agreement with the theory. The effect of the feed-flow rate on the peak resolution in shown in Figure 5. An increased feed-flow results in an increased band width. Broadening the peaks means decreasing the resolution, which is confirmed by the experiment and the theory (14).

The effect of the eluent flow-rate on the resolution is shown in Figure 6. The eluent flow-rate was varied between 11 and 18 ml/min. The resolution between mannitol and sorbitol is lower then predicted. This is mainly due to the fact that linear isotherms are

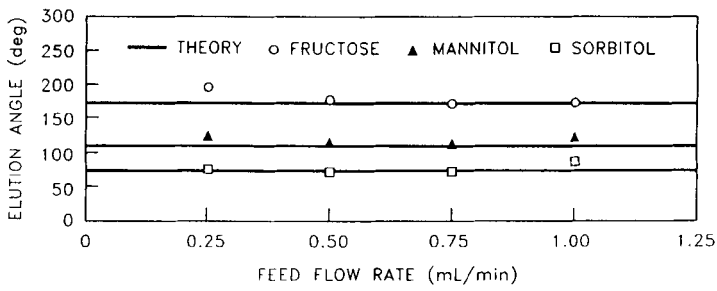

Figure 4. Comparison of experimental and theoretical concentration profiles for the continuous separation of a sugar mixture (28).

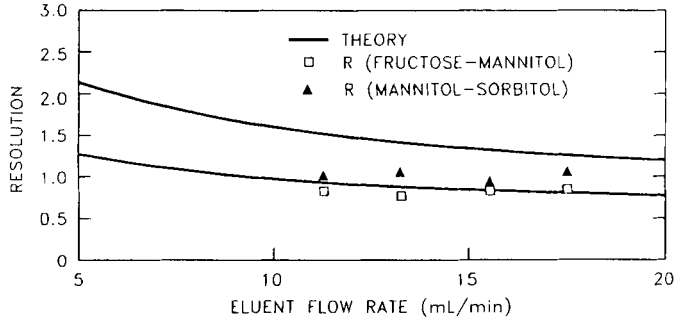

Figure 5. Comparison of experimental and theoretical concentration profiles for the continuous isocratic separation of a mixture of albumin and hemoglobin (23).

assumed. Stronger retained species show broader peaks which decreases the resolution significantly. Overall, the model which assumes linear isotherms is sufficient for mixtures containing up to 75g/l of the discussed carbohydrates. Other studies (9, 18) have shown that for short retention times, which are characteristic of fructose, glucose and sucrose, the theory predicts linear behavior up to 250 g/L, but for higher retention times , such as are characteristic of mannitol and sorbitol, a modification to take account of dispersion and non-linearities in the isotherms may be needed. For separation of industrial mixtures of the three carbohydrates modeling based on the assumption of

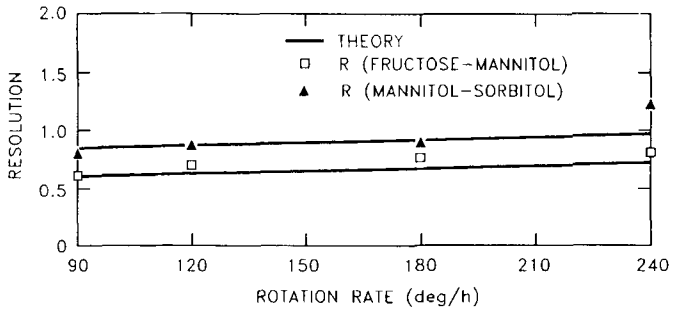

Figure 6. Comparison of experimental and theoretical concentration profiles for the continuous step-wise elution separation of a mixture of albumin and hemoglobin. The salt concentration step is from 0 to 150 mM in a 10 mM phosphate buffer at pH 6.5.

linear isotherms may not suffice, and more work with non linear isotherms such as Freundlich or Langmuir may be required. More experimental work would be required to validate which isotherms would be required and whether competition plays a role at higher concentrations. The theoretical foundation exists for including dispersion into the theoretical prediction.

It is obvious that the separations of fructose, sorbitol and mannitol is efficiently achieved by chromatographic means. Application to a process environment will require some optimization. The linear theory can be used as a simple framework to predict behavior up to moderate concentrations and feed rates.

NOTATION

c	....	liquid phase solute concentration [g/l]
$c^{\times}$	....	equilibrium solute concentration [g/l]
c_F	....	feed solute concentration [g/l]
K	....	distribution coefficient dimensionless
$k_0 * a$	....	global mass-transfer parameter $[s^{-1}]$

z	....	bed length [cm]
ε	....	bed void fraction
θ	....	displacement from feed point [deg]
ω	....	rotation rate [deg/h]

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