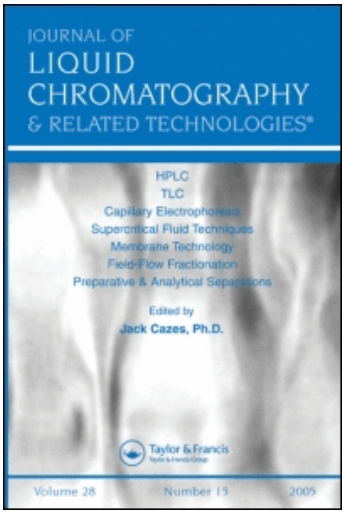


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# A Novel Chromatographic Production Scale Separation Process for L-Fucose

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**Abstract:** There is an increasing interest towards a special and very rare sugar, L-fucose, because of its functionalities, i.e., in the human body. There are only a few industrial production processes for L-fucose, and chromatographic separation of this valuable component from hemicellulose hydrolysates could be a feasible alternative. However, chromatographic separation of L-fucose with sufficient purity from other monosaccharides, especially deoxy sugars, has presented a problem in the state of the art. The aim of this work was to find a new process scale chromatographic purification method for L-fucose containing liquor. Of special interest was a process suitable for recovery of L-fucose from plant based biomass hydrolysate. This paper presents an industrial scale chromatographic separation method for the production of L-fucose. The use of a combination of strong and weak acid cation exchange resins increases L-fucose purity gradually, while the use of strong base anion exchange resin gives an excellent separation of L-fucose from other remaining sugar compounds.

**Keywords:** Anion exchange resin, Bisulfite, Cation exchange resin, L-Fucose, Production scale chromatography, Rare sugars

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## INTRODUCTION

L-fucose (6-deoxy-L-galactose) is a rare sugar that belongs to the family of deoxy sugars. Rare sugars in this context are monosaccharides and their derivatives existing in natural biopolymers, but in limited quantities. Often, their production volumes are low, and they are expensive. In nature, both optical isomers of fucose are widely found.[1] Conformations of the D and L forms are presented in Figure 1. Interest in L-fucose and L-fucose containing oligosaccharides has increased in the medical field as more information of the role of fucose in biological functions has been published. For example, recent studies have indicated that L-fucose and L-fucose rich oligo- and polysaccharides could be used as anti-ageing aids,[2–4] and that they inhibit immuno allergic reactions on the skin.[5] In addition, L-fucose has been shown to facilitate long term memory formation.[6] The role of L-fucose in disorders like diabetes, cancer, and inflammatory diseases is under research.



L-fucose is known to be found widely in biomass, especially in plant biomass, but in minor amounts. Generally, there are three sources for L-fucose: oligo- and polysaccharides, glycoproteins, and glycolipids. Currently, only oligo- and polysaccharides are commercially important in the production of L-fucose. In plant material, L-fucose is typically associated with polysaccharides, which are often highly branched structures having L-fucopyranosyl units either at the ends of or within the polysaccharide chains. In the intercellular mucilage of seaweeds, there are also L-fucose polysaccharides. They are often composed of sulfated L-fucose polymers known as fucoidans.[7]

There are, however, several concepts to synthesize L-fucose: chemical, microbiological, and enzymatic. Other sugars, like L-arabinose,[8] D-galactose,[9–11] D-glucose,[12] methyl-L-rhamnose,[13] and D-mannose[14] can be used as raw materials for the chemical synthesis of L-fucose. Production of L-fucose by synthetic means leads to multi-step processes with relatively low L-fucose yield. Microbiological syntheses of L-fucose are based on fermentation using micro-organisms, which produce

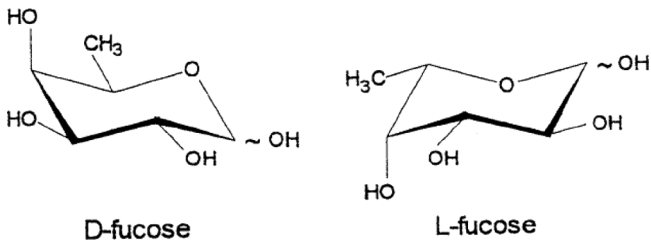


*Figure 1.* Chair structures of L- and D-fucose.

L-fucose-containing exopolysaccahrides (EPS). L-fucose can be released by chemical or enzymatic hydrolysis and then recovered from the hydrolysate. Possible fucose producing strains are *E. amnigenus*[15,16] and *Clavibacter michiganensis* LMG 5604,[7] which produces an EPS known as clavan. One multi-step enzymatic method to produce L-fucose is published.[17]

Some algae types are an alternative source for L-fucose. Polyfucose can be hydrolyzed to L-fucose, which can be crystallized after purification. Several authors have reported and patented methods for manufacturing L-fucose from seaweeds.[18–20] They differ in algae type, extraction, and hydrolysis methods as well as in process yields.

Materials like wood, straw, and by-products from agriculture and food industry contain hemicelluloses, which are heteropolysaccharides consisting mainly of pentose and hexose sugars. Monomeric sugars, for example D-xylose, D-mannose, D-glucose, L-arabinose, L-fucose, and L-rhamnose, can be obtained by acid hydrolysis. Hemicellulose hydrolysates containing monosaccharides can be fractionated by large scale chromatographic separation. Typically, hydrolysates contain one or more sugars of interest. Trees, such as birch or beech, are good raw materials for these kinds of hydrolysis. Spent sulfite liquor obtained from acid pulping process is one of the industrially available hydrolysates. It is the source for raw material in this study, also.



## INDUSTRIAL SCALE CHROMATOGRAPHIC SEPARATION OF CARBOHYDRATES ON ION EXCHANGE RESINS

Chromatographic separation of carbohydrates has been used on an industrial scale since the 1960s. Desugarization of beet molasses, production of high fructose syrup from corn based glucose syrup, and xylose recovered from hardwood based spent liquors are examples of processes, where charged polystyrene-divinylbenzene (PS-DVB) resins are used.[21,22] Recently, chromatographic separation of rare sugars like rhamnose and mannose has gained interest. Mannose, for example, can be recovered using barium ($Ba^{2+}$) form strong acid cation (SAC) exchange resin with other resin ion forms.[23] Efficient separation of rhamnose from some monosaccharides like xylose is achieved with weak acid cation (WAC) exchange resin at elevated pH.

It is assumed that more hydrophobic saccharides, such as deoxy-, methyl-, and anhydrosugars, are retained less on the WAC exchange resin in sodium form than more hydrophilic saccharides.[24] The acrylic resin matrix of WAC exchange resin is inherently more hydrophilic than in the PS-DVB structure due to a lower amount of hydrophobic benzene groups. Hydrophobic-hydrophilic interactions, thus affect the separation of components, in addition to other phenomena like size exclusion and ion exclusion.

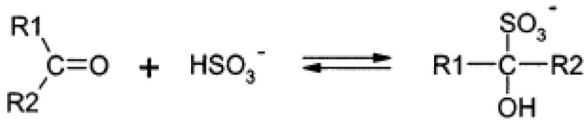


*Figure 2.* Bisulfite addition – a characteristic reaction of carbonyl compounds.

The use of strong base anion (SBA) exchange resin in bisulfite form was used for sugar separation on analytical scale already in the 1950s. It was found that some sugars, like glucose and fructose, having carbonyl groups can effectively be separated from each other.[25] Different methods for selective recovery of low amounts of carbonyl group containing compounds from organic solutions are also presented in literature. Addition of bisulfite ion makes carbonyl groups undergo a nucleophilic addition reaction with bisulfite (see Figure 2).[26,27] This can be utilized together with an ion exchange membrane or adsorption on a polymeric reagent or electrophoresis to separate carbonyl containing groups. Reaction of bisulfite with carbonyl groups explains good separation between aldehydes and ketoses on SBA exchange resin in bisulfite form.

Chromatographic separation of L-fucose from plant based biomass hydrolysates has been challenging. The recovery of deoxy sugars, e.g., rhamnose and fucose, from one another has especially been a problem due to their closely related molecular structures. These deoxy sugars are often recovered as a mixture in the same fraction. The novel chromatographic separation process, presented in this paper, solves this problem and makes it possible to separate L-fucose from other monosaccharides including deoxy sugars. This purification process is especially suitable for sugar solutions, where the separation of sugars from each other by any other method is relatively difficult or even impossible.



## EXPERIMENTAL

### Materials and Methods

#### Raw Material

The origin of the raw material used in this study was spent sulfite liquor. The raw material in these tests was a fucose enriched fraction after xylose and rhamnose recovery.

The composition of the liquor was analyzed by HPLC to contain 47.2% on dry matter (DM) various sugars (fucose, rhamnose, xylose, arabinose, xylulose), and sugar like compounds such as methyl-α-D-xylopyranoside (MAX) (Table 1). On DM, 52.8% were unidentified

***Table 1.*** Feed solution composition of the untreated raw material (DM refers to dry matter)

| Component | Composition % on DM |
|---|---|
| Fucose | 6.9 |
| Rhamnose | 14.3 |
| Xylose | 2.2 |
| Arabinose | 2.9 |
| Xylulose | 3.6 |
| Methyl-α-D-xylopyranoside | 17.3 |
| Others | 52.8 |

compounds consisting of inorganic and organic components, like other carbohydrates. Exact composition of the raw material was not analyzed.

The raw material DM content was adjusted to 35 wt% before chromatographic separation. The feed liquid pH was adjusted to 6.5 with 50 wt% sodium hydroxide, because most organic acids are dissociated at this pH and can be separated as their salts from neutral components with SAC exchange resin. In addition, suspended solids were removed by filtration with Seitz plate and frame filter using diatomaceous earth (Kenite 300) as filter aid; body feed (0.5% DM) and precoat (1 $kg/m^2$).



## Chromatographic Separation Parameters

The chosen column filling materials to be used were SAC exchange resin in sodium form, WAC exchange resin in sodium form, and SBA exchange resin in bisulfite form. SAC exchange resin in sodium form enables separation of salts and neutral sugars due to ion exclusion phenomenon. WAC exchange resin was expected to separate MAX, the single most common component in the feed solution, from the mixture because MAX is a more hydrophobic component compared to other sugars present. SBA exchange resin in bisulfite form was believed to separate some of the unknowns, since if they had no carbonyl groups, separation should be relatively effective.

The aim of the chromatographic separation tests was to estimate the technical viability of the fucose recovery process. Final optimization was not done at this stage. Therefore, the parameters for the chromatographic separation steps were typical values for industrial scale batch separation processes. Characteristics of the applied resins and chromatographic separation parameters used in the experiments are presented in Table 2.

*Table 2.* Separation resin characteristics and chromatographic separation process parameters

| Resin type | Strong acid cation SAC | Weak acid cation WAC | Strong base anion SBA |
|---|---|---|---|
| Ion form | $Na^+$ | $Na^+$ | $HSO_3^-$ |
| Resin name | Finex CC 11 GC | Finex CS 16GC | Finex AS 532 GC (type II) |
| Cross-linking, DVB-% | 5.5 | 8 | 3.5 |
| Bead size, mm | 0.33 | 0.33 | 0.35 |
| Capacity, eq/L | 1.5 | 2.7 | 1.0 |
| Column inner diameter, m | 1.0 | 0.6 | 0.6 |
| Resin bed height, m | 4.8 | 5.2 | 4.8 |
| Temperature, °C | 65 | 65 | 40 |
| Flow rate, L/h | 550 | 150 | 283 |
| Feed volume, L | 150 | 60 | 100 |
| Feed dry matter content, g/100 g | 35 | 32 | 36 |
| Number of feeds prior to fraction series collection | 2 | 2 | – |



## Analysis Methods

Dry matter (DM) content was measured via refractive index (RI) (Index Instruments, model GRP 11-37). From the measured RI values, the dry matter content was determined according to concentration vs. RI conversion tables specific to the most occurring sugar in the solution. The sucrose based conversion table was used, if the amount of the unknowns exceeded the amount of the main component.

Conductivity and pH were measured with The Mettler Toledo Rondolino, SevenMulti S47.

The sugar composition of the samples was analyzed with Agilent Technologies 1100 HPLC system equipped with an amino ($NH_2$) column (Asahipak, Phenomenex) and a refractive index (RI) detector. The HPLC column was 250 mm long, and the inner diameter was 4.6 mm. Column filling material particle size was 5 μm. Analyses were carried out at 55°C, the flow rate was 0.8 mL/min, and the eluent composition was 79% acetonitrile (HPLC grade) in which 50% $H_3PO_4$ (Fisher) 1.6 mL/L was used. Before injection (20 μL) all samples were filtered through a 0.2 μm membrane (Acro, Gelman Sciences). Quantification of sugars was made using an external standard method. Standard materials were methyl-α-D-xylopyranoside (INC Biomedicals Inc.), L(+)-rhamnose

monohydrate (Fluka), D(−)-arabinose (Fluka), D(+)-fucose (Sigma-Aldrich), D(+)-xylose (Sigma-Aldrich).

## RESULTS AND DISCUSSION

### Tests with Strong Acid Cation Exchange Resin in Sodium Form

The raw material described in Table 1 was subjected to a chromatographic separation step where the column filling material was SAC exchange resin in sodium form. Separation conditions are presented in Table 2. Figure 3 presents the results of the analyses (pH, conductivity, sugar composition) of the samples from the fraction series collected at 5 min from the outlet of the column.

As expected, ionic compounds are eluted in the front part of the separation profile. This can be seen in the measured conductivity profile. Rhamnose, arabinose, and xylose are the first identified sugars. which start to elute after the conductivity peak. Fucose, xylulose, and methyl-α-D-xylopyranoside (MAX) are completely overlapping, and they are not separated from each other. At the end of the profile unknown compounds are again abundant.



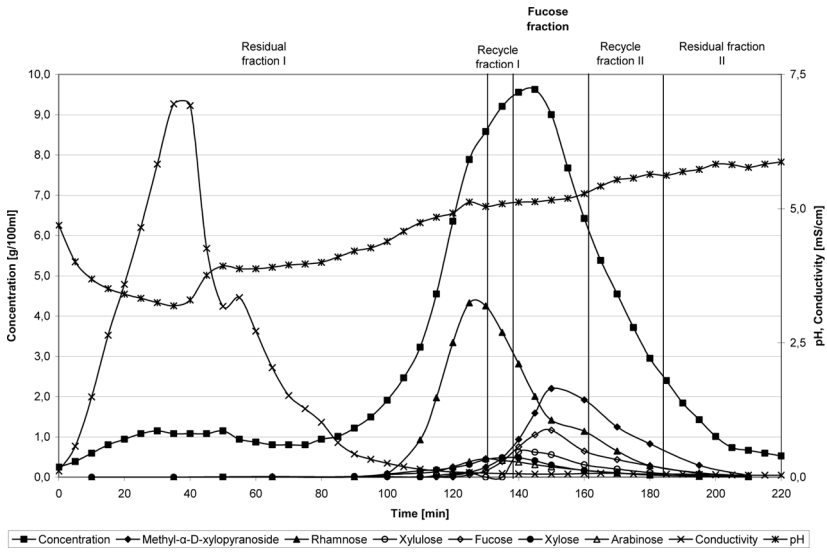


*Figure 3.* Chromatographic separation profile: SAC exchange resin in sodium form.

The cut points of the fractions were adjusted in order to achieve a good removal of ionic components and rhamnose, and simultaneously maintaining a high yield for fucose. In order to keep fucose yield high, recycle fractions were collected before and after the fucose fraction in all chromatographic separation steps of the process. In industrial scale processes, recycle fraction(s) could be used for dilution of the feed material and/or used as additional recycle feed solution, which is fed to the column before or after the actual feed.

Fraction compositions with the used cut points (Figure 3) are presented in Table 3. Fucose content in the feed solution was ca 7% on DM, and fucose content ca 11% on DM was achieved, in average, in the product fraction. Fucose yield from feed directly to product fraction was ca 59%.

Main impurities in the fucose fraction are still rhamnose and MAX. Fucose fractions from several repeated cycles were combined, concentrated by evaporation, and subjected to the next chromatographic separation step, where WAC exchange resin in sodium form was used as column filling material.



## Tests with Weak Acid Cation Exchange Resin in Sodium Form

The aim of the second separation step using WAC exchange resin in sodium form was to separate fucose from MAX, rhamnose, and other remaining components. The feed solution was the fucose fraction from

***Table 3.*** Fraction volumes, concentrations, sugar composition (fucose, rhamnose and methyl-α-D-xylopyranoside) and component yields. SAC exchange resin in sodium form

| | Residual fraction I | Recycle fraction I | Fucose fraction | Recycle fraction II | Residual fraction II |
|---|---|---|---|---|---|
| Volume, L | 1238 | 92 | 229 | 229 | 275 |
| Concentration, g/100 mL | 2.0 | 9.6 | 7.8 | 3.2 | 0.8 |
| Composition | | | | | |
| Fucose, % on DM | 0.5 | 5.9 | 10.9 | 8.9 | 3.6 |
| Rhamnose, % on DM | 28.4 | 33.3 | 17.1 | 11.0 | 4.9 |
| Methyl-α-D-xylopyranoside, % on DM | 0.9 | 7.4 | 23.9 | 26.0 | 11.5 |
| Yield | | | | | |
| Fucose, % | 3.8 | 15.8 | 58.8 | 19.2 | 2.4 |
| Rhamnose, % | 50.4 | 21.1 | 22.0 | 5.7 | 0.8 |
| Methyl-α-D-xylopyranoside, % | 3.1 | 8.9 | 58.7 | 25.7 | 3.5 |

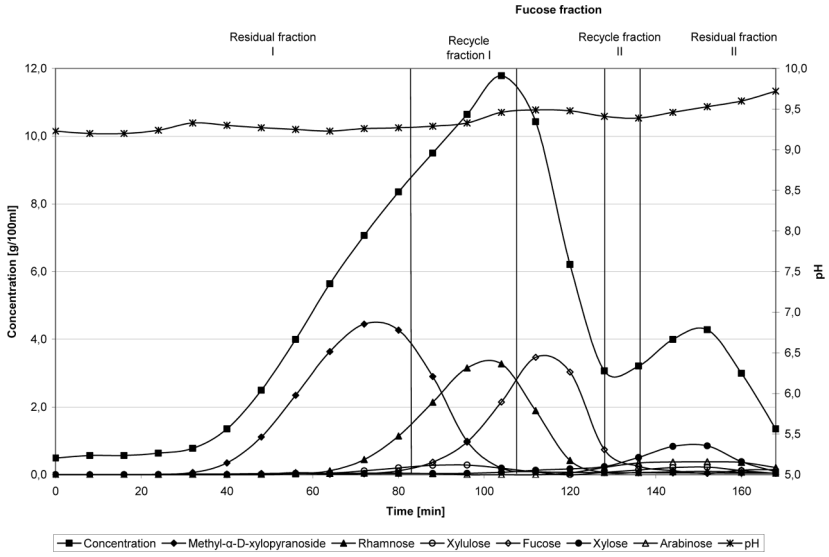


*Figure 4.* Chromatographic separation profile: WAC exchange resin in sodium form.

the first chromatographic separation step. Separation parameters and resin characteristics are presented in Table 2. Figure 4 presents the results of the analyses (pH, sugar composition) of the samples from the fraction series collected at 8 min intervals from the outlet of the column.

MAX elutes as the first component, and is followed by deoxy sugars, fucose, and rhamnose. The first concentration peak consists mostly of MAX, fucose, and rhamnose and the second of arabinose, xylose, galactose, mannose, fructose, and glucose. Table 3 presents data of the collected fractions from the WAC ($Na^+$) chromatographic separation. Fucose content in the feed solution was ca 11% on DM, and fucose content ca 38% on DM was achieved in average in the product fraction. Fucose yield from feed directly to product fraction was ca 50%.

In order to keep WAC exchange resin in sodium form, prevalent pH has to be above 7.[28] It is known, that sugars are degraded at high pH. It was not, however, analyzed here how fucose reacts under alkaline conditions. After the chromatographic separation and before evaporation, fucose fraction pH was, however, adjusted down to 4.5 by 32 wt% HCl.

## Tests with Strong Base Anion Exchange Resin in Bisulfite Form

The feed solution to the column, filled with SBA exchange resin in bisulfite form, was a mixture of fucose fraction from the previous, second

***Table 4.*** Fraction volumes, concentrations, sugar compositions (fucose, rhamnose and methyl-α-D-xylopyranoside) and component yields. WAC exchange resin in sodium form

| | Residual fraction I | Recycle fraction I | Fucose fraction | Recycle fraction II | Residual fraction II |
|---|---|---|---|---|---|
| Volume, L | 225 | 63 | 50 | 25 | 78 |
| Concentration, g/100 mL | 3.0 | 10.7 | 6.2 | 3.2 | 3.1 |
| Composition | | | | | |
| Fucose, % on DM | 1.2 | 14.0 | 38.2 | 8.7 | 3.5 |
| Rhamnose, % on DM | 6.6 | 26.1 | 10.8 | 2.1 | 2.4 |
| Methyl-α-D-xylopyranoside, % on DM | 49.5 | 10.1 | 1.2 | 1.8 | 1.5 |
| Yield | | | | | |
| Fucose, % | 3.4 | 39.9 | 50.1 | 3.0 | 3.7 |
| Rhamnose, % | 17.4 | 67.0 | 12.7 | 0.7 | 2.3 |
| Methyl-α-D-xylopyranoside, % | 81.6 | 16.3 | 0.9 | 0.4 | 0.9 |



chromatographic separation step and runoff from fucose crystallization tests. The feed solution composition is presented in Table 5, and the separation parameters and resin characteristics in Table 2.

Figure 5 presents the results of the analyses (pH, sugar composition) of the samples from the fraction series collected at 10 min intervals from the outlet of the column. There are two separate concentration peaks, of which the first one contains significant amounts of unidentified compounds and minor amounts of MAX and xylulose. The chromatographic separation is very good for the unidentified compounds and fucose. It can be seen that rhamnose elutes after fucose and that decreases the fucose content at the end of the profile.

Chromatographic separation using SBA exchange resin in bisulfite form as column filling material requires different parameters compared to the first and second chromatographic separation steps. Because of extremely great retardation of aldehydes and ketoses to the resin, a

***Table 5.*** Feed solution composition. SBA exchange resin in bisulfite form

| Component | Composition % on DM |
|---|---|
| Fucose | 47.9 |
| Rhamnose | 10.5 |
| Arabinose | 2.2 |
| Others | 39.4 |

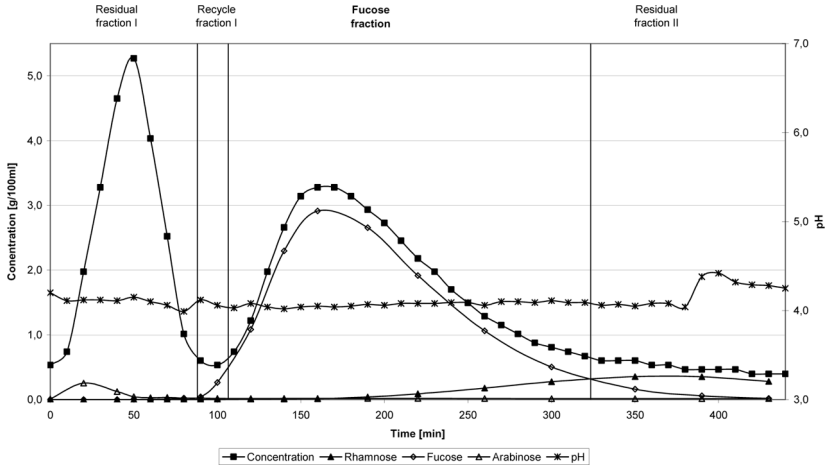


***Figure 5.*** Chromatographic separation profile: SBA exchange resin in bisulfite form.



large feed size and a faster flow rate were used. Separation temperature was as low as 40°C, because generally SBA exchange resins are thermally less stable than SAC resins and higher temperature can increase degradation.

Fraction volumes, concentrations, sugar compositions, and yields for fucose and rhamnose are presented in Table 6. After the third chromatographic separation step with SBA exchange resin in bisulfite form the fucose fraction was further purified by ion exchange prior to crystallization.

***Table 6.*** Fraction volumes, concentrations, sugar compositions (fucose, rhamnose) and component yields. SBA exchange resin in bisulfite form

| | Residual fraction I | Recycle fraction I | Fucose fraction | Residual fraction II |
|---|---|---|---|---|
| Volume, L | 450 | 146 | 980 | 980 |
| Concentration, g/100 mL | 2.6 | 0.6 | 1.9 | 0.5 |
| Compostion | | | | |
| Fucose, % on DM | 0.2 | 40.3 | 82.6 | 20.8 |
| Rhamnose, % on DM | – | – | 6.4 | 70.2 |
| Yield | | | | |
| Fucose, % | 0.1 | 1.9 | 94.7 | 3.3 |
| Rhamnose, % | – | – | 39.6 | 60.4 |

## Ion Exchange and Crystallization

Removal of ionic and color compounds before crystallization improves crystal quality and can also be used for preventing odor problems in the final product. The evaporated fucose fraction contained cations (mainly sodium from the chromatographic separation exchange resins) and anions (mainly sulphate and sulphite). They were removed by anion and cation exchange resins (Amberlite IRA 252, Amberlite IRA 92). Activated carbon (Chemviron CPG) was also used to remove color.

Fucose was crystallized from a solution purified by ion exchange. Crystallization is typically carried out using a solvent selected from water, alcohol, and mixtures thereof. Alcohol may be, e.g., ethanol because it is a preferable solvent in the food and pharmaceutical industry compared to other alcohols. Fucose crystallization was carried out by using water and ethanol as solvents, and crystals were recovered by filtration and washed with ethanol.

Before crystallization, the fucose solution was concentrated by evaporation to 80 wt%. In the beginning of the boiling crystallization step the solution was seeded with fucose crystals. Ethanol was added after cooling the crystallization mass to room temperature. The crystallization mass was then allowed to stand for four days at room temperature, after which the crystals were recovered by filtration and washed with ethanol.



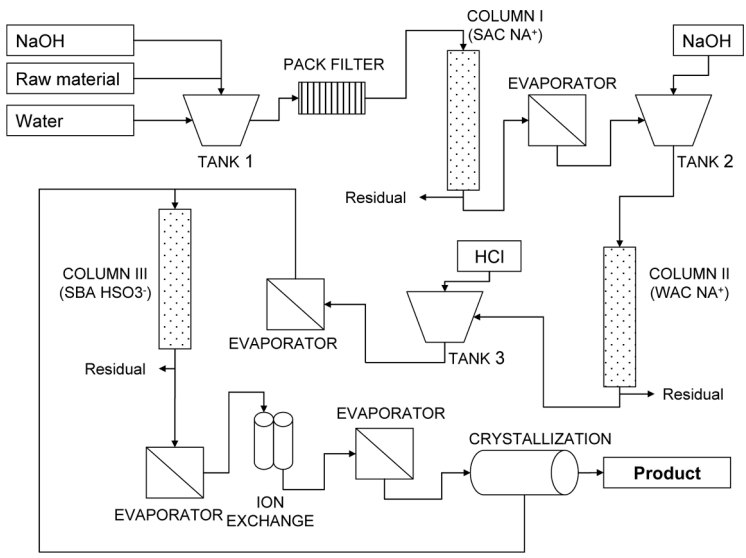


***Figure 6.*** Schematic picture of the L-fucose production process.

Crystals with a high purity, >99%, were obtained. To increase the crystallization yield, a second crystallization step could be made from the mother liquid. For the crystallization step, the total yield for fucose was estimated to be 70%.

A schematic picture of the presented process (three chromatographic separation steps, ion exchange, purification, and crystallization) is presented in Figure 6.

## CONCLUSIONS

A new recovery process for fucose, starting from hemicellulose hydrolysate and including a new chromatographic separation sequence, was developed. The process consists of three chromatographic separation steps. In the first chromatographic separation step (SAC exchange resin in sodium form), most of the ionic compounds are removed from neutral components. In the second chromatographic step (WAC exchange resin in sodium form), methyl-α-D-xylopyranoside and xylose are separated from fucose. In the last, third chromatographic separation step (SBA exchange resin in bisulfite form), a very good separation for fucose from other sugars is achieved. Separation capacity and fraction concentrations are, however, relatively low compared to the first and second chromatographic separation steps. Ion exchange purification is beneficial before crystallization. Combination of the three chromatographic steps is needed, depending on the sugar and ion composition of the raw material.

The presented process sequence has been tested on an industrial scale, and found to be technically viable. There is still need for optimization, however. For example, the maximum total yield over the unit operations can be found studying the process as a whole, and by sub optimizing each step separately.

## LIST OF ABBREVIATIONS

| | |
|---|---|
| DM | dry matter |
| MAX | methyl-α-D-xylopyranoside |
| PS-DVB | polystyrene-divinylbenzene |
| RI | refractive index |
| SAC | strong acid cation (exchange resin) |
| SBA | strong base anion (exchange resin) |
| WAC | weak acid cation (exchange resin) |
| wt% | weight percentage |

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