

Development of a Continuous Lactulose Process: Separation and Purification[†]

Michael F. Kozempel,* Michael J. Kurantz, James C. Craig, Jr., and Kevin B. Hicks

We developed a continuous pilot plant process to produce lactulose from lactose using boric acid to boost the conversion to about 75%. The process consists of three reactors (two continuous stirred tank reactors followed by a tubular reactor), pH adjustment, a crystallizer-filter-evaporator recycle initial separation section, and a chromatographic purification system to produce lactulose containing less than 1–5 ppm of boric acid. The continuous process operates at 0.53 kg/min (20% solids) through the reactors and about 0.3 kg/min (55% solids) out of the initial separation section. The chromatographic separation is at the prep scale with a flow rate of 2.0 mL/min. The final product is a 55% solids syrup containing no detectable boric acid.

Introduction

Lactulose, a synthetic ketose disaccharide, is a high-valued pharmaceutical with worldwide markets. Lactulose is normally synthesized by alkaline isomerization of lactose, a process that produces lactulose in low yields due to numerous side reactions (Lobry de Bruyn and Ekenstein, 1895; Montgomery and Hudson, 1930).

The use of a complexation reagent such as boric acid (Hicks and Parrish, 1980; Hicks et al., 1981) shifts the pseudo-equilibrium established during base-catalyzed isomerization in favor of lactulose and prevents degradative side reactions. Hicks (1981) and Hicks et al. (1983) showed that treatment of aldoses, such as lactose, with boric acid in a molar ratio of 1:1 in the presence of tertiary amines produces lactulose in high yields and that the tertiary amine can be replaced by NaOH (Hicks et al., 1983, 1984).

We are developing a commercially feasible process to produce lactulose based upon the use of the borate ion and NaOH to isomerize lactose. The first step in this study was the development of a model for the kinetics of the isomerization reaction (Kozempel and Kurantz, 1994a) followed by the development of a pilot plant reactor system (Kozempel and Kurantz, 1994b).

This paper presents the results of our efforts to develop a pilot plant process to produce a commercially feasible lactulose product from the reaction mixture.

Experimental Procedures

Figure 1 shows the pilot plant process flow sheet including the reactor system (Kozempel and Kurantz, 1994b). The feed rate was 0.53 kg/min.

The initial separation process follows adjustment of the pH of the product from the reactors (Figure 1). In the pilot plant, it was expedient to adjust the pH by adding HCl directly to the cooled reaction mixture. The product contained the NaCl. Commercially, the pH adjustment would be made by ion exchange chromatography to minimize the salt content of the product. The major pieces of equipment are a crystallizer, filter, and evaporator. The crystallizer was a 227-L scraped wall kettle,

Hamilton style A, double-motion Teflon scraper agitator (Hamilton Copper and Brass Works Co., Hamilton, OH). The filter was a Sparkler Filter, size 8–3 (Sparkler Manufacturing Co., Conroe, TX), fitted with polypropylene multifilament #5-41F411 filter cloth manufactured by Tetko, Inc. (Lancaster, NY). The evaporator was a conical Kontro Ajust-o-film 0.093 m² evaporator (Peter-sham, MA).

Final removal of boric acid was by liquid chromatography using a Spectra-Physics HPLC system at low pressure, <4000 kPa. It consisted of a Spectra-Physics SP8700 control module, SP8750 pump, SP6040 differential refractometer, and SP4270 integrator. We used in-house packed prep columns, 300 × 25 mm (Bio-Rad, Richmond, CA).

Results and Discussion

The two references by Kozempel and Kurantz (1994a,b) present the development of the continuous chemical reaction system. The product from the reactors was 20% solids containing 15% boric acid (dry weight basis, dwb). Lactulose is normally sold as a syrup containing about 55% solids. The boric acid permitted in lactulose syrup is in the range of 1–5 ppm. Therefore, it was necessary to remove virtually all of the boric acid and concentrate the product.

Some boric acid can be crystallized from the reaction product after evaporation to concentrate the solids. However, the solution becomes very viscous and impossible to filter satisfactorily. The key to successfully removing boric acid efficiently by crystallization is continuous operation. By removing the boric acid solids continuously the slurry never gets too viscous. In a sense, a differential amount of boric acid is fed and removed in each pass. The solubility of boric acid in water is 2.3 wt % at –3 °C (Technical data sheet IC-11). However, the solubility of boric acid in this system is affected by the complexing with lactulose. At basic pH the complex is very strong. Although it apparently breaks under acidic conditions, there appears to be some attractive forces still present or an equilibrium concentration for the complex. To test this hypothesis we prepared solutions of boric acid and of HCl with the initial pH adjusted to be approximately the same. We added increasing amounts of lactulose to each solution. With HCl nothing happened; there is no complex formed between lactulose and HCl. With boric acid the pH

* To whom correspondence should be addressed.

[†] Reference of brand or firm names does not constitute an endorsement by the U.S. Department of Agriculture over others of a similar nature not mentioned.

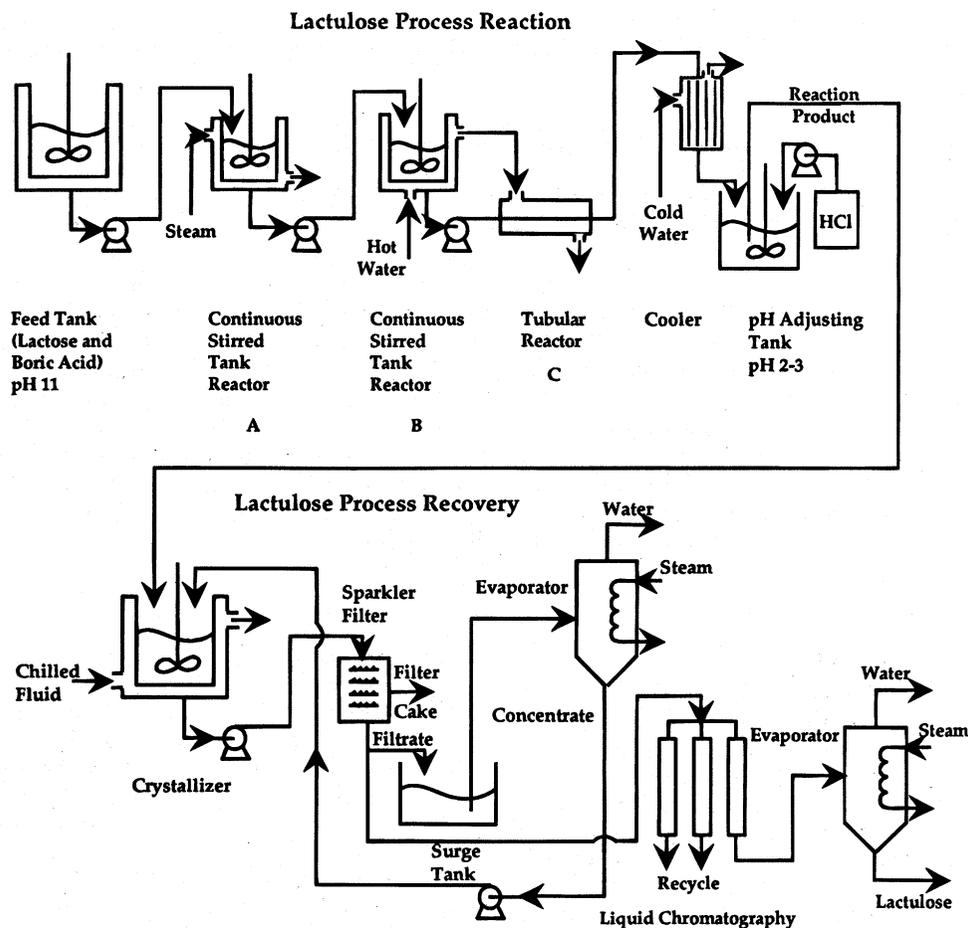


Figure 1. Continuous pilot plant flow sheet.

dropped (Figure 2). The drop in pH indicates a complexation of boric acid with lactulose. The plot indicates that the separation should be run below pH 3 to maximize crystallization.

By starting with fresh reactor product (solids concentrations at 20%), we varied the pH of the feed in the crystallizer. Table 1 shows the results. As the pH dropped, the boric acid content of the filtrate dropped, confirming the previous finding that the recovery should be run below pH 3. At pH 2.8 and -3°C in the crystallizer, the steady state boric acid concentration is 7% (dwb).

Boric acid crystallizes as needles which are easy to filter. The filtrate from the Sparkler filter was clear with no evidence of undissolved solids. Referring to Figure 1, the flow sheet, consider the crystallizer as the start-up feed tank, although there are continuous feed and recycle to the crystallizer. Before start-up, the feed solution in the crystallizer was chilled to about -1°C . After this temperature was reached, we began the process by pumping the solution through the Sparkler filter. The filtrate went to the evaporator to concentrate the solution further. The concentrate was then recycled to the crystallizer.

Ideally, fresh feed would be started to the crystallizer to maintain volume until the system reached steady-state operating conditions. In a practical sense, in the pilot plant, we processed discreet batches, over a period of days, to achieve steady-state conditions. The "product" of the previous day's run became the feed for the next run with fresh makeup feed to bring the crystallizer to volume. As the feed to the evaporator (filtrate from the filter) approached 55%, the solids content of the concentrate approached 75%. The rotor seized just beyond this

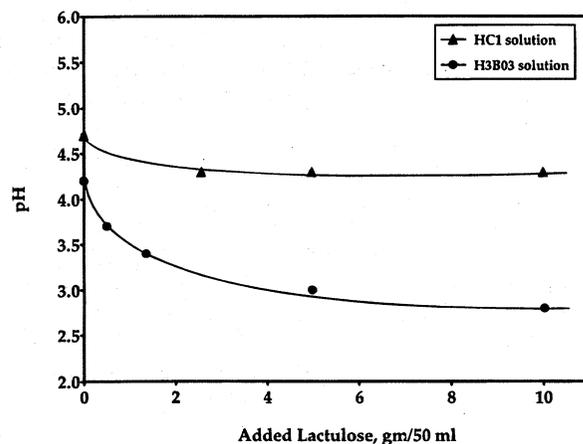


Figure 2. Interaction of the lactulose-boric acid complex with pH.

Table 1. Effect of pH on Crystallization

pH	product (filtrate)	
	4.5	41% solids
3.7	42% solids	10% boric acid
2.8	48% solids	7% boric acid

point. When the feed to the evaporator reached about 60%, the viscosity of the concentrate increased dramatically, stalling the rotors in the evaporator. The goal is to run the evaporator as close as possible to the limit to maximize crystallization without stalling or fouling the evaporator. Practically, this is with an evaporator feed of 55% solids. Feeding fresh reactor product to the crystallizer maintains the desired solids concentration during steady-state operation.

Table 2. Experimental Process Flow Rates and Concentrations

filtrate		conc	rate, kg/min			
%solid	%H ₃ BO ₃	%solids	feed	filtrate	conc	product
55	4.3	67	0.26	1.4	1.20	0.28
59	4.7	68	0.40	1.6	0.60	0.28
57	4.7	78	0.40	1.7	1.14	0.30
57	4.1	60	0.42	1.7	1.14	0.44

Table 2 lists the process flow rates and concentrations at continuous operation. Table 3 lists the process operating parameters. Because we measured and controlled flow manually, we achieved a pseudo steady state with no product removal. However, because the product rate was so low relative to the recycle rate, we upset the process each time we collected product. To achieve steady state will require a continuous filter, automatic control, and scale-up. Hence the flow rates in Table 2 approximate a mass balance. The continuous operation runs lasted up to 2.25 h. When the filter pressure reached about 650 kPa, we terminated the runs.

As shown in Table 2, the effluent from this recovery process is nominally 4% boric acid (dwb) or 2.2% in a 55% syrup. The boric acid concentration must be 1–5 ppm. We investigated several potential methods to reduce the boric acid concentration to 1–5 ppm syrup. These included ultrafiltration, leaching, melting, ion exchange, electro dialysis, and supercritical fluid extraction. None worked.

We tried ligand exchange chromatography, used successfully in the analytical chemistry laboratory to separate lactose, boric acid, and reaction byproducts. Initial pilot plant studies were directed to determining a packing which would split the lactulose–boric acid complex and separate the key components, lactulose and boric acid. Resin Dowex 99CA/320, from the Dow Chemical Co., Midland, MI, was used.

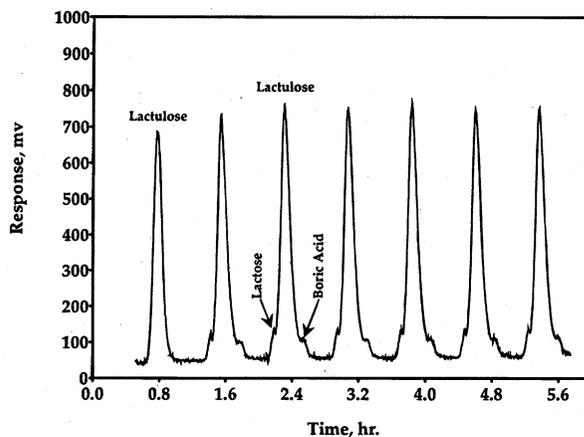
As test solutions we used a nominal 20% lactulose solution, a saturated boric acid solution, and a solution of the reactor product containing 55% solids, diluted with 3 parts deionized water (DIW).

The chromatograms using DIW as the mobile phase looked virtually identical to chromatograms using deionized water, adjusted to pH 2, as the eluent (pH 2). Run separately, the retention time for lactulose was 44 min and for boric acid was 54 min. The boric acid peak begins at the maximum in the lactulose peak. Although boric acid exhibits a stronger chromatographic absorption, it has a weaker response.

Actual reaction product gave an earlier peak, presumably lactose. The boric acid peak was apparently obscured by the lactulose peak. Assuming lactulose and boric acid were split but not well separated, we collected fractions from the onset of the peaks until the maximum of the lactulose peak. The samples were evaporated to about 6% solids on a steam bath and analyzed for boric acid. The DIW-eluted product had 590 ppm boric acid. This is over 5000 ppm for a 55% syrup of lactulose. No boric acid was detected in the pH 2-eluted product.

Apparently this packing with pH 2 splits the complex. Unfortunately the components are not well separated and much of the lactulose elutes with the boric acid. With DIW, the complex is not sufficiently split and/or separated.

We added a second column, a size exclusion column to separate the already split complex into its components. The second column was HW-40C, size exclusion resin (Supelco, Bellefonte, PA). The particle size was 50–100 μm .

**Figure 3.** Two-column chromatogram for pilot plant run showing lactose, lactulose, and boric acid for seven consecutive samples (one reference sample of lactulose and six samples of reaction product).**Table 3. Separation Process Parameters**

Crystallizer	
<i>U</i>	4230 cal/(m ² °C min)
area	1.22 m ²
agitator	25 rpm
Filter	
area	0.09 m ²
Evaporator	
<i>U</i>	27856 cal/(m ² °C min)
area	0.09 m ²
rotors	495 rpm
clearance	0.16 cm
steam	21 kPa
temp	26 °C
abs pressure	4.1 kPa

Using a 2 mL/min flow rate, we collected lactulose fractions from the onset (41 min) of the lactulose peak (46 min) until 8 min past the peak (54 min). The evaporated fractions contained no detectable boric acid. Figure 3 shows a chromatogram for one of the pilot plant runs (multiple injections) using two chromatography columns. For reference, the first injection was lactulose. The subsequent samples were reaction products injected at intervals planned to maximize recovery of product. Note the single peak for lactulose (first peak) and the leading and following peaks (lactose and boric acid) for the subsequent products.

Although the present separation was conducted on a semipreparative-scale column capable of resolving only milligram quantities of sugars, this basic technology has been readily scaled up to larger scale laboratory (Hicks and Sondey, 1987; Barker and Thawait, 1983) and commercial-size (Weiss, 1987) devices. In the latter case, the use of moving bed and simulated moving bed technology is currently used for the multiton scale separations of fructose and glucose during refining of high-fructose corn syrups. Similar technology could be used for the industrial-scale separation of lactulose.

Conclusion

A continuous pilot plant process was developed to produce lactulose by the isomerization of lactose under basic conditions with boric acid used to shift the equilibrium in favor of lactulose. Conversion is about 75%. Most of the boric acid is removed initially in a recycle crystallization process. The remaining boric acid is removed by liquid chromatography.

Literature Cited

- Acree, T. E. The chemistry of sugars in boric acid solution. In *Carbohydrates in solution*; Isbell, H. S., Ed.; *Advances in Chemistry Series 117*; American Chemical Society: Washington, DC, 1971; pp 208-219.
- Barker, P. E.; Thawait, S. *Chem. Ind.* **1983**, 7, 817-821.
- Hicks, K. B. Ketose sugars from aldose sugars. U.S. Patent 4,273,922, June 16, 1981.
- Hicks, K. B.; Parrish F. W. A new method for preparation of lactulose from lactose. *Carbohydr. Res.* **1980**, 82, 393-397.
- Hicks, K. B.; Sondey, S. M. *J. Chromatogr.* **1987**, 389, 183-194.
- Hicks, K. B.; Symanski, E. V.; Pfeffer, P. E. Synthesis and high-performance liquid chromatography of maltulose and cellobiulose. *Carbohydr. Res.* **1983**, 112, 37-50.
- Hicks, K. B.; Raupp, D. L.; Smith, P. W. Preparation and Purification of Lactulose from Sweet Cheese Whey Ultrafiltrate. *J. Agric. Food Chem.* **1984**, 32, 288-292.
- Hicks, K. B.; Simpson, G. L.; Bradbury, A. G. W. Removal of boric acid and related compounds from solutions of carbohydrates with a boron-selective resin (IRA-743). *Carbohydr. Res.* **1986**, 147, 39-48.
- Kozempel, M. F.; Kurantz, M. F. The isomerization kinetics of lactose to lactulose in the presence of borate. *J. Chem. Technol. Biotechnol.* **1994a**, 59 (1), 25-29.
- Kozempel, M. F.; Kurantz, M. F. A continuous reactor system for production of lactulose. *J. Chem. Technol. Biotechnol.* **1994b**, 59 (3), 265-269.
- Lobry de Bruyn, C. A.; Van Ekenstein, W. A. *Recl. Trav. Chim.* **1895**, 14, 203.
- Montgomery, E. M.; Hudson, C. S. Relations between rotary power and structure in the sugar group. XXVII. Synthesis of a new disaccharide ketose (lactulose) from lactose. *J. Am. Chem. Soc.* **1930**, 52, 2101-2106.
- Technical data sheet IC-11. United States Borax & Chemical Corp., 3075 Wilshire Blvd., Los Angeles, CA, 1983.
- Weiss, M. D. *Ind. Chem.* **1987**, 8, 16-20.