006371

Simulated Scale-up and Cost Estimate of a Process for Alkaline Isomerization of Lactose to Lactulose Using Boric Acid as Complexation Agent

Michael Kozempel,* Andrew McAloon & Lorie Roth

US Department of Agriculture,† Agricultural Research Service, Eastern Regional Research Center, 600 East Mermaid Lane, Wyndmoor, PA 19038, USA

(Received 9 May 1996; revised version received 9 August 1996; accepted 2 September 1996)

Abstract: A continuous pilot plant process for converting lactose to lactulose, using boric acid as a complexation agent was previously developed. To appraise the commercial feasibility of the process, a scale-up to a commercial plant using the ERRC Food Process Simulator, a process simulator developed at the Eastern Regional Research Center was projected and a cost estimate made. The cost to produce a 55% lactulose syrup at a rate of 93 kilograms per hour (563 359 kg year^{-1}) was \$5.20 per kilogram (\$2.36 per pound). These costs, which do not include packaging or distribution expenses, do include a 25% return on the plant investment.

Key words: lactulose, simulation, scale-up, cost

INTRODUCTION

Lactulose is a pharmaceutical with world markets of 20 000 tons per year.[1] It is a non-caloric, complex carbohydrate synthesized from milk sugar (lactose), a surplus by-product of the dairy industry. The principal world-wide outlets are as a laxative and for treatment for portal systemic encephalopathy. In Japan and Europe it is used in infant formulas and as a health food since it induces growth of non-pathogenic bacteria in the colon. In Europe it is an over-the-counter drug; in the United States, a prescription drug.

Normal synthesis is by alkaline isomerization of lactose with low yields and side reactions.[2,3] Boric acid acts as a complexation agent[4,5] which shifts the equilibrium, giving conversions of 75% and higher. Based on this research the reaction kinetics was determined for the boric acid complexation reaction,[6] a continuous reaction section developed and continuous separation and purification for a continuous pilot plant process developed.[7,8]

* To whom correspondence should be addressed.

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

The objectives of this study were two-fold; (1) to estimate the costs for a commercial lactulose plant, and (2) to demonstrate the application of the ERRC Food Process Simulator to a non-food process. Based on the data from the pilot plant process, this paper presents the results of a simulated scale-up to a commercial plant, using the ERRC Food Process Simulator,[9] and a cost estimate for a projected commercial plant.

2 EXPERIMENTAL

Experimental data for a pilot-scale facility were previously reported.[6–8]

The process was simulated with the ERRC Food Process Simulator,[9] which is a computer program for calculating mass and energy balances for continuous processes. The simulator was developed at the Eastern Regional Research Center. It is compiled using Microsoft FORTRAN 4.1 and runs under MS DOS 3.0 or higher, but requires a math coprocessor and 640 kb RAM. It is free to domestic users.

Figure 1 is a flow sheet of the pilot plant process. The first section was the reaction consisting of three reactors in series. The first two were equal sized Continuous Stirred Tank Reactors (CSTR-A and CSTR-B) followed

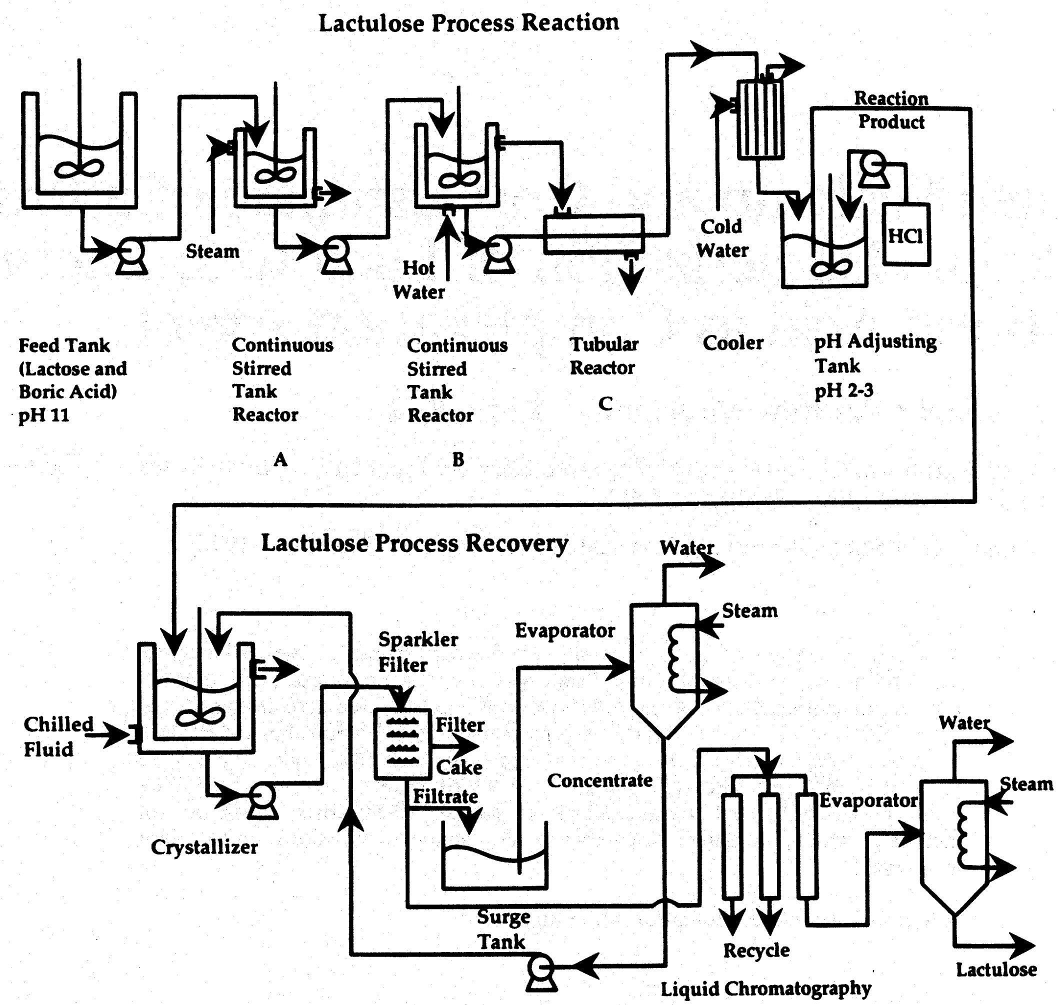

Fig. 1. Pilot plant process flow sheet for lactulose.

by a double-pass tubular reactor (TR-C). With this configuration the conversion of lactose to lactulose is 75% with a total dwell time in the reactors of approximately 1·5 h.[7] The small finishing reactor enables this configuration to give the same yield as a batch reactor.[7] The tubular reactor accounted for 5·4% of the reaction time. A batch reactor suffers from the liability of batch to batch variation, inefficiencies due to filling and emptying the reactors and increased size or number of reactors. A single plug-flow reactor should require the same time as a batch reactor—about 90 min. This would be much too large to be practical.

After cooling and acidifying the product to pH 2–3, there was a preliminary separation of boric acid. (The final product must contain no more than 1–5 ppm boric acid.) 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. This preliminary separation section consisted of a crystallizer, filter and a scraped surface evaporator. Part of the concentrate from the evaporator was recycled to the crystallizer. Hence nucleation was ample in the crystallizer. The filter removed boric acid crystals. The effluent from this recovery process was nominally 4% boric acid, dry weight basis. As a 55% syrup, the normal article of commerce, the boric acid concentration would be 2·2% on an 'as is' basis. Since the boric acid concentration must be 1–5 ppm further processing was required.

A two-column chromatographic separation was used. The first column resin was Dowex 99CA/320 (protonated with the mobile phase which was deionized water acidified to pH 2) and the second column resin was HW-40C, size exclusion. The first column split the lactulose–boric acid complex and the second column separated the components. Using 300 mm prep columns with 2 cm^3 min^{-1} flow rate, lactulose fractions contained no detectable boric acid.

The flow in the pilot plant reaction section was 31·8 kg h^{-1}. However, the flow rates in the preliminary separation and final purification sections were lower. The flow in the preliminary separation section was chosen as the base case for simulation. The pilot plant process with a flow rate through the reactors of 24·0 kg h^{-1} was simulated and then scaled up to a feed rate of 389 kg h^{-1} (lactulose product rate of 93 kg h^{-1} at 55% solids). Costs were computed with the ASPEN PLUS 8.5 cost package. (The simulation could have been performed using ASPEN by programming in custom models for the process. However, one of the objectives was to demonstrate the application of this simulator program to a nonfood process. The ERRC Food Process Simulator is a specialized program for food and food related processes. It is free to domestic users. ASPEN is a powerful, expensive program capable of simulating most processes with custom models.)

3 RESULTS AND DISCUSSION

3.1 Simulation

The ERRC Food Process Simulator was written using a potato flake process as the prototype. Therefore, most of the unit operations models developed were not applicable to a pharmaceutical plant. To adapt it required adding new models, i.e. reactor, crystallizer, filter, evaporator and chromatography. As originally conceived, new models would be added to the program when applied to new processing plants. Instructions for doing this are included in the program. However, it is much simpler to substitute new models. In this particular case, many of the models do not apply to the lactulose process. Therefore, the following substitutions were made; reactor for hot water blancher, crystallizer for hot water blancher with ideal mixing, filter for steam peeler, evaporator for lye peeler and chromatography for spray washer.

The models are not general but rather specific to the lactulose/boric acid process. The reactor model included the specific kinetics for the lactose to lactulose isomerization,[6] with the appropriate coefficients for the rate equation and Arrhenius equation.[6,7] Boric acid crystallizes readily into needles. In this process the solubility, and its interaction with the other components, is the controlling mechanism and not the kinetics of crystallization. Therefore, the crystallizer model used the following equation for the solubility curve for boric acid in water[10] to calculate the quantity of boric acid crystallized.

$$\mathrm{Sol} = \exp(10{\cdot}05 - 2491{\cdot}9/T)$$

where Sol = wt% boric acid and T = temperature, (K).

Since this was not a pure boric acid/water system but a system with interactions from the other components, a small correction factor, −0·019, adjusted the calculated values to agree with experimental data in the crystallizer. The soluble and insoluble boric acid were considered separate components of the exit stream going to the filter. The filter model removed the insoluble boric acid. The evaporator model was written using an ideal energy balance, no heat losses.[8] The chromatography columns were modelled based on an experienced vendor's design using our experimental data. Using the design separation, the model splits the stream as instructed. Hence, this unit operations model would more appropriately be called a splitter.

For the base case, the process simulation used the pilot plant studies as previously reported[6–8] and shown in Fig. 1. Using the revised ERRC Food Process Simulator program, the process was simulated at 389 kg h^{-1} feed. Figure 2 shows the simulation flow sheet and Table 1 presents the flow rates and compositions of the important carbohydrate containing streams. Stream 21, the filter cake, would normally be recycled to reactor A. Also, the 'waste' stream, 41, which contains higher molecular weight and colored byproducts plus some boric acid and lactulose, would be treated to recover lactulose and boric acid and recycled to the chromotagraphy columns. Neither option was included in the cost estimate because it had not been done experimentally. However, anticipating that the 'waste' stream would be recycled to the chromotagraphy columns, it was concentrated to 9% solids, which is the approximate concentration in the columns.

3.2 Cost estimate

Based on the simulation of a commercial plant, the cost to produce a 55% lactulose syrup at a rate of 93 kilograms per hour (563 359 kg $year^{-1}$) was estimated at \$5.20 per kilogram (\$2.36 per pound). These costs, which do not include packaging or distribution

TABLE 1
Simulated Process Flow Streams

Stream	*Flow* ($kg\ h^{-1}$)	*Solids (conc.)*	*Lactulose (conc.)*	*Boric acid (conc.)*	*Lactose (conc.)*	*By-product (conc.)*
Feed (1)	389	0·23	—	0·03	0·20	—
Product (43)	93·2	0·55	0·54	—	0·01	—
Filter cake (21)	14·1	0·83	0·14	0·64	—	0·05
Waste (47)	316	0·09	0·02	0·01	—	0·06

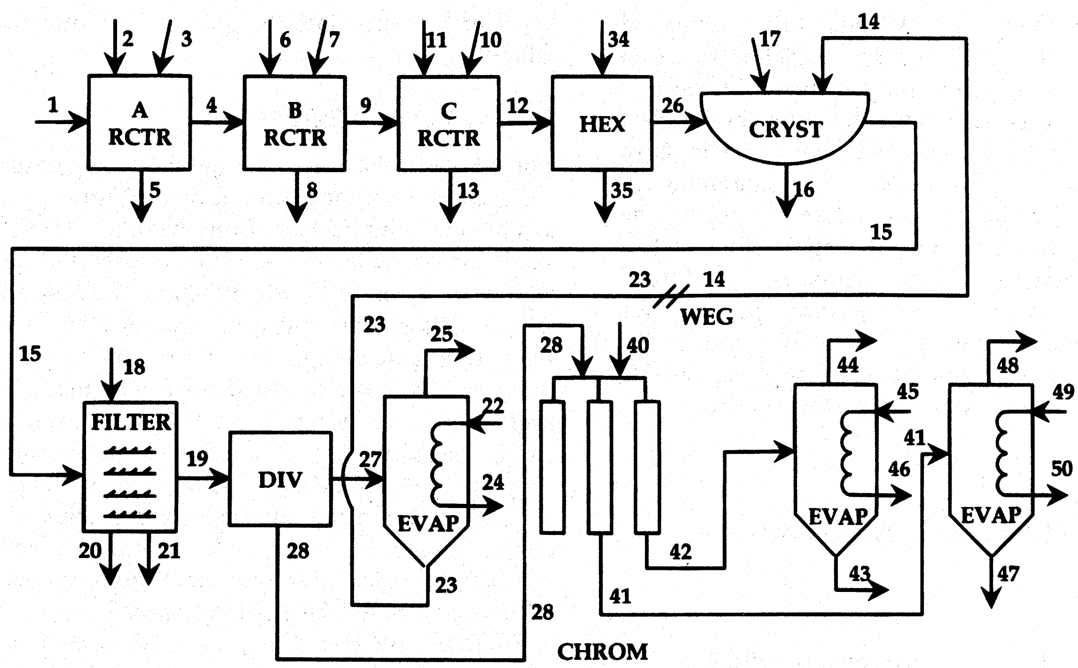

Fig. 2. Simulation flow sheet for the lactulose process.

expenses, do include a 25% return on the plant investment. A summary of these costs is presented on Table 2. Table 2 is for cost estimating purposes only, not for design.

Production costs were also determined for similar facilities with capacities ranging from 45 kg h^{-1} to 450 kg h^{-1}. The changes in the cost of raw materials and utilities are proportional to changes in the production rate; the capital costs change at a rate less than the changes in the production rate and the labor costs remain relatively constant. The results are shown in Fig. 3 which plots the cost to produce as a function of production capacity. As shown in the figure, the cost to produce approaches \$3.40 per kg as an asymptotic limit. The value corresponding to the plant size reported here, 93 kg h^{-1}, is on the low end of the curve at \$5.20 per kg.

3.3 Investment costs

The investment cost of the processing facility to produce a 55% lactulose syrup was developed from the information represented in Fig. 1. The equipment prices which are in Table 2 were obtained from equipment suppliers and internal sources. These prices were then used to calculate total installed cost values through the use of installation factors[11] which convert the supply costs of equipment to total installed equipment costs. This total installed equipment cost also includes the equipment installation cost and the cost of all required piping, electrical and other material for a functioning unit.

The equipment costs for lactulose production facilities have been grouped into three categories, equipment costs for the lactose–lactulose reactions area, equipment

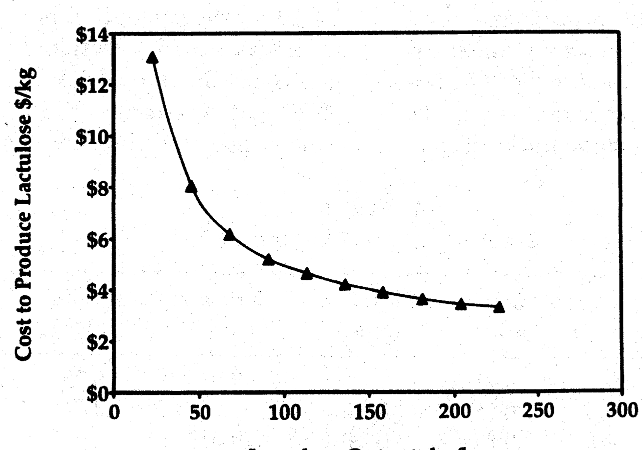

Fig. 3. Cost as a function of production capacity.

TABLE 2
Investment Costs

Description	*Cost ($)*
Equipment costs (FOB plant)	
Reactions area	
Raw material feed and mixing equipment	58 000
Reactor A equipment	19 000
Stirred reactor 0·61 m dia. × 1·52 m long	
Reactor B equipment	18 000
Stirred reactor 0·53 m dia. × 1·52 m long	
Reactor C and heat exchanger equipment	34 000
Tubular exchanger—5 min residence time	
Heat exchanger Area = 2·97 m^2	
pH adjustment equipment	16 000
Tank capacity = 1 h holding time	
Subtotal, Reactions area equipment	145 000
Separations area	
Crystallizer	82 000
Total inlet and recycle flow = 1692 kg h^{-1}	
Filter system	38 000
Filter area = 1·50 m^2	
Pre chromatography evaporator	102 000
Surface area = 1·50 m^2	
Chromatography equipment and resin	581 000
Inlet feed = 151 kg h^{-1}	
Post-chromatography evaporators	156 000
Surface area = 41·34 m^2	
Lactulose storage equipment	11 000
Two tanks at 8 h capacity each	
Subtotal, Separations area equipment	970 000
Utilities area	
Compressed air supply	26 000
Subtotal, Utility equipment	26 000
Equipment supply costs (FOB plant)	1 141 000
Installation and construction material costs	2 156 000
Contingency	494 000
Total installed costs	3 791 000
Working capital	455 000
Start-up charges	129 000
Total investment charges	4 375 000

costs for the lactulose separations area and utility equipment costs that are common to both areas. The equipment cost was estimated at approximately $144 000 for the lactose–lactulose reaction system, $970 000 for the lactulose separation system and $26 000 for utility equipment. The additional cost to install the equipment and furnish a plant ready to operate is $2 157 000.

There are additional capital costs for those general or overhead items common to both the reactions and the separations area. Start-up costs which include 2 months of training for the plant operators and maintenance staff were estimated at $129 000. Working capital which was based on the parameters in Table 3 was estimated at $455 000. In addition, a contingency allowance of $494 000 to cover unforeseen occurrences has been included to give a total investment cost of $4 375 000.

3.4 Operating costs

Operating costs have been developed for a production schedule of twenty four hours a day, two hundred and fifty two days per year. The operating costs include charges for plant labor, raw materials, utilities, maintenance, operating supplies and general plant overhead. An allowance for depreciation of the plant facilities has also been incorporated into the plant operating costs.

Plant labor costs are based on a five person operating staff per shift. One operator is included to handle the loading and blending of the lactose, water and boric acid. A second operator controls the remaining work in the reactions area, including pH adjustment. A third operator is included to oversee the crystallizer, filter and initial evaporator. The fourth operator will be assigned to the chromatography unit and the remaining evaporators. The fifth operator will handle any remaining tasks and function as a team leader. A two-person maintenance crew is scheduled on the day shift and one person on each of the remaining two shifts. In addition, one supervisor per day is included in the plant operating & maintenance force. Plant labor costs account for 30% of the operating expenses.

Raw material and utility costs have been calculated and are shown on Table 4. The raw material, utility and catalyst replacement costs are roughly 25% of the annual operating costs. The lactose, boric acid, HCl and NaOH unit pricing is from the *Chemical Marketing Reporter*, 8/24/94. Water and electricity prices are generic 'average' prices that will vary from area to area. Steam pricing is a generic price that will vary from plant to plant. The chromatography resin columns have

TABLE 3
Basis for Working Capital Calculations

Raw materials inventory	40 days
In process materials inventory	5 days
Finished products inventory	14 days
Plant materials and supplies	3% capital costs
Accounts receivable	60 days of production cost excluding depreciation
Accounts payable	40 days of production cost excluding depreciation
Operating cash	30 days of operating costs less depreciation

TABLE 4
Raw Material and Utility Requirements

Material	*Unit cost ($)*[a]	*Annual cost ($)*
Water	0·00079 kg^{-1}	3200
Lactose	0·5218 kg^{-1}	246 000
HCl	0·094 kg^{-1}	10 000
Boric acid	0·9682 kg^{-1}	31 000
Sodium hydroxide	1·313 kg^{-1}	125 000
Electricity	0·000019 kJ^{-1}	43 600
Steam	0·004409 kg^{-1}	25 900
Chromatography resin	66·62 dm^{-3}	100 000

[a] Price escalated to third quarter, 1995.

a volume of 1500 dm^3 and contain equal parts of two resins, Dowex 99CA/320 and Supelco HW-40C. The annual catalyst cost is based on vendors' private quotations and on replacing 50% of both catalysts each year.

The chromatography unit that splits and separates the lactulose and boric acid has an initial resin fill with a value of approximately $200 000. Assuming resin replacement once every 2 years, a $100 000 a year charge is included in the plant operating expenses for resin replacement.

Other production expenses include plant overhead charges, operating and maintenance supplies and depreciation expenses. Plant production overhead charges are included for general and administration expenses, property taxes and insurance fees. These overhead charges contribute 14% to the plant operating costs. Operating supplies and maintenance material charges are another 6% of the plant operating costs. A 7 year straight line depreciation has been used to determine operating cost and taxable depreciation has been calculated based on a 7 year MACRS [Modified Accelerated Cost Recovery System] schedule for 20% of the plant operating expenses.

3.5 Economic factors

The cost to produce lactulose includes a 25% return and an allowance of 12% of revenue for corporate sales and administration overhead. This and the other economic factors used in the calculations are shown in Table 5.

3.6 Future

Although a continuous pilot plant process was developed, scale-up simulated and the costs estimated, there are still several important issues not addressed. For instance, to simplify the pilot plant research, the reactor product was acidified with HCl. The product contains neutralization salt, which is not desirable. The preferable method is ion exchange using a packing such as IR 120P. It works but has not been integrated into the continuous pilot plant process.

In the pilot plant process a batch filter removed boric acid for recycle to the reactors. Conversion to a continuous filter, including filter cake washing, remains to be reduced to practice. What effect will impurities in the recycle have on the reactors?

Ion exchange chromatography to split the complex and separate the product is the rate controlling step in the process. It will require the greatest scale-up both in size and uncertainty. There will probably be scale-up inefficiencies associated with larger flow rates and columns. However, commercial processes already exist which separate similar sugars.

Of course, the purpose of this study was to present data to evaluate the commercial potential of the process. This paper gives an estimate of the costs to make lactulose by this process. The only data available are from the pilot plant. Granted, there will be scale-up inefficiencies, not only with the chromatography columns and evaporator, but with the other units as well, for example in the reactors. Most of the inefficiencies should be evaluated at the next level of scale-up, before commercialization. Another scale-up is justified to get a better assessment.

TABLE 5
Economic Factors

Internal rate of return	25%
Economic life	7 years
Depreciable life	7 years
Corporate tax rate	35%
Salvage value	0%
Debt fraction	50%
Construction interest rate	8% per year
Long term interest rate	8%
Escalation rate	4% per year
Corporate—administration and sales costs	12% of plant revenues

4 CONCLUSIONS

The commercial synthesis of lactulose from lactose using boric acid was determined to be economically competitive. For a plant producing 562 500 kg of 55% lactulose syrup (the article of commerce), with a 25% rate of return on plant investment, the cost to produce is $5.20 per kg.

The ERRC Food Process Simulator was demonstrated to be applicable to non-potato process plants. By substituting models for unit operations specific to the lactulose plant, it was possible to simulate the pilot plant and predict a commercial scale plant.

REFERENCES

1. Tamura, Y., Mizota, T., Shimamura, S. & Tomita, M., Lactulose and its application to the food and pharmaceutical industries. In *Proceedings of the IDF Workshop on Lactose Hydrolysis. Bulletin* **289** (1993) chapter 10, pp. 43–53.
2. Lobry de Bruyn, C. A. & van Ekenstein, W., *Alberda*, Action des alcalis sur les sucres, II Transformation réciproque des uns dans les autres des sucres glucose, fructose, et mannose. *Rec. Trav. Chim. Pays-Bas*, **14** (1895) 203–216.
3. 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.*, **52** (1930) 2101–6.
4. Hicks, K. B., Ketose sugars from aldose sugars. US Patent 4,273,922, June 16, 1981.

5. Hicks, K. B. & Parrish, F. W., A new method for preparation of lactulose from lactose. *Carbohydr. Res.*, **82** (1980) 393–7.
6. Kozempel, M. F. & Kurantz, M., The isomerization kinetics of lactose to lactulose in the presence of borate. *J. Chem. Tech. Biotech.*, **59**(1) (1994) 25–9.
7. Kozempel, M. F. & Kurantz, M. F., A continuous reactor system for production of lactulose. *J. Chem. Tech. Biotech.*, **59**(3) (1994) 265–9.
8. Kozempel, M. F., Jr, Kurantz, M., Craig, J. C. & Hicks, K. B., Development of a continuous lactulose process—separation and purification. *Biotechnol. Prog.*, **11**(3) (1995) 592–5.
9. Kozempel, M. F., Tomasula, P. & Craig, J. C. Jr, The development of the ERRC Food Process Simulator. *J. Simulation Practice and Theory*, **2** (1995) 221–236.
10. Technical data sheet I C-11. United States Borax & Chemical Corp. 3075 Wilshire Blvd., Los Angeles, CA. 1983.
11. Hand, W. E., Capital costs from process flow sheets. *AACE Cost Engineers Notebook*, American Association of Cost Engineers, Morgantown, West Virginia, 1992.