

# A Continuous Reactor System for Production of Lactulose

Michael Kozempel\* & Michael Kurantz

Engineering Science Unit, Eastern Regional Research Centre, ARS, United States Department of Agriculture, 600 East Mermaid Lane, Philadelphia, Pennsylvania 19118, USA

**Abstract:** A continuous reactor process was developed to produce lactulose from lactose. A system of two CSTRs in series with a tubular finishing reactor gave conversion to lactulose of about 76%. The reactors ran at 71–75°C with a volumetric hold-up in the CSTRs of 22.7 dm<sup>3</sup> and in the tubular reactor of 2.6 dm<sup>3</sup>. Each CSTR had a nominal residence time of 44 min. The flow rate was 0.53 dm<sup>3</sup> min<sup>-1</sup>.

Key words: lactulose, lactose, boric acid, reaction model, process.

## NOTATION

$C$	Concentration
$C_0$	Initial concentration
$C_j$	Concentration in $j$ th backmix reactor in series
$ILS$	Lactulose, lactulose concentration
$j$	Number of backmix reactors in series
$k_1$	Rate constant for disappearance of lactose (min <sup>-1</sup> )
$L$	Lactose, lactose concentration (moles unit volume <sup>-1</sup> )
$L_0$	Initial lactose concentration (moles unit volume <sup>-1</sup> )
$L_{\infty}$	Lactose concentration at equilibrium (moles unit volume <sup>-1</sup> )
$T$	Absolute temperature (K)
$\theta$	Time (min)
$\theta_0$	Volumetric reactor holdup/flow rate (min)
$\tau$	Dwell time (min)

## INTRODUCTION

Lactulose is a complex carbohydrate, highly valued as a pharmaceutical with world-wide markets. It is normally synthesised by isomerisation of lactose. In the presence of base (pH 11) lactose isomerises to lactulose in low

yield with multiple side reactions giving by-products. Boric acid forms a complex with lactulose at high pH. Under acidic conditions the complex breaks. Hicks and coworkers<sup>1,2</sup> showed that treatment of lactose with boric acid in a molar ratio of 1:1 in the presence of tertiary amines produces lactulose in high yields. The use of boric acid as a complexation reagent shifts the equilibrium established during base-catalysed isomerisation in favor of lactulose and retards degradative side-reactions. The process allows for recovery and recycling of reagents; a technique which increases the efficiency of the procedure. They<sup>2,3</sup> also showed that NaOH can be substituted for the tertiary amines.

As previously reported,<sup>4</sup> the isomerisation of lactose to lactulose was modeled as two consecutive but separate reactions. The first was considered the equilibrium conversion of lactose to a boric acid–lactulose complex plus galactose and other by-products through competing first order reactions. (The complex is stable under basic conditions.) The second reaction was the disruption of the complex, releasing lactulose, when the mixture was acidified. The rate controlling reaction is the isomerisation of lactose to lactulose in the presence of NaOH and the formation of a boric acid–lactulose complex. The reaction kinetics were modeled as a first order disappearance of lactose, eqn (1).

$$dL/d\theta = -k_1L$$

$$\text{where } k_1 = [8.389 \times 10^{18}] \exp[-16095/T].$$

\* To whom correspondence should be addressed.  
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A temperature range of 70–75°C appears to give the highest equilibrium conversion. The kinetics model, eqn (1), applies at pH 11.0 and a molar ratio of boric acid to lactose of 1.0. The equilibrium conversion is about 75%.

A commercially feasible process is under development to make lactulose based on the boric acid complexation reaction. The process will consist of a reactor system involving several continuous reactors, a preliminary separation system to remove the bulk of the boric acid, and a final purification of the product. It is the goal of this research to develop a continuous pilot plant process and the data needed for scale up to a commercial process. Having developed the kinetics model, this paper presents the results of the next step—the development of a continuous reactor system.

## EXPERIMENTAL

Figure 1 shows the reactor system. The reactor system consisted of three reactors in series. The first two were continuous stirred tank reactors (CSTR-A and CSTR-B) followed by a double pass tubular reactor (TR-C). Each CSTR had a 22.7 dm<sup>3</sup> hold-up volume. The volume of the tubular reactor was 2.6 dm<sup>3</sup>. Flow through the reactor process was with Zenith metering pumps, size 11. In an alternative version of the process a centrifugal pump connected CSTR-B and TR-C. The reaction mixture to CSTR-B was recirculated to create very high agitation by using a recycle stream and a throttling valve.

From the tubular reactor the discharge went to a sanitary plate and frame heat exchanger to cool the product stream below room temperature with tap water as the cooling medium.

Enough feed (140 dm<sup>3</sup>) was charged to the feed kettle to supply the reactors for approximately 4.5 h at a rate of 0.53 dm<sup>3</sup> min<sup>-1</sup>. The feed tank was first filled to level with water and the lactose added with agitation. Then boric acid was added. While still agitating to keep the solids in suspension, NaOH was added to adjust the pH. It takes about 1.4 dm<sup>3</sup> 50% NaOH to raise the feed mixture to pH 11.0. Most of the lactose dissolved when

the pH reached about 9.5. A small amount remained undissolved.

Lactose was edible grade purchased from Swiss Valley Farms Co., Davenport, IA (USA). The lactose was the monohydrate form. Results were corrected for water of hydration. Boric acid was NF granular purchased from US Borax, US Borax & Chemical Corp., Los Angeles, CA (USA).

Samples for analysis were placed in an ice–water bath and the carbohydrate composition determined using HPLC with refractive index detection.

## RESULTS AND DISCUSSION

Based on the reaction kinetics model, the reaction was scaled up to an 18.9 dm<sup>3</sup> batch reactor to compare data with the laboratory batch results. The pH was adjusted to 11.0. The molar ratio of boric acid to lactose was 1.0. After two hours reaction time the conversion to lactulose was 71–74% which compares favorably to the laboratory equilibrium conversion of 75%.

Using the model, a continuous reactor process was developed. Integrating the kinetics model, eqn (1), gives;

$$L/(L_0 - L_\infty) = \exp(-k_1\theta) \quad (2)$$

where  $\theta$  = reaction time and  $k_1 = 0.041 \text{ min}^{-1}$  at 71°C.

(As shown later, the best reaction conditions found are 44 min residence time per reactor at 71°C and about 30 rpm in the first CSTR.) At 71°C, in a batch reactor, the kinetics model predicts the product mixture will reach 97.4% of the equilibrium value in 88 min.

The actual concentration of reactant and product in a flow reactor such as CSTR is a function of mixing as well as reaction. For a perfectly mixed first order flow reactor (CSTR) the concentration of product mixture in the exit stream follows eqn (3).<sup>5</sup>

$$C/C_0 = \exp(-\theta/\theta_0) \quad (3)$$

where  $\theta/\theta_0$  = reduced dwell time.

Equation (3) permits the comparison of a batch reactor with a CSTR of equivalent nominal residence time. According to eqn (3), the effluent composition from a

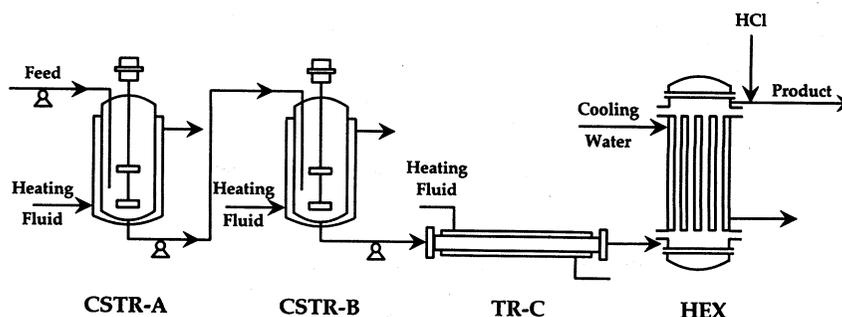


Fig. 1. Schematic of the continuous reactor system showing two continuous stirred tank reactors (CSTRs), a tubular reactor (TR) and a heat exchanger (HEX).

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perfectly mixed continuous stirred tank reactor of nominal dwell time ( $\theta_0$ ) 88 min at a dwell time ( $\theta$ ) of 88 min is 36.8% unreacted feed (C, lactose) and 63.2% product mixture. An equivalent batch reactor with a reaction time of 88 min would have reached 97.4% of equilibrium (from the reaction model). Therefore, the 63.2% of feed to the CSTR which entered into reaction would have reached 97.4% of equilibrium with the equilibrium value for lactulose of 75%. The effluent from the CSTR (63.2% product mixture plus 36.8% unreacted feed) would contain only 46.2% lactulose ( $0.632 \times 0.974 \times 0.75$ ). Hence, a single CSTR with perfect mixing, would reach a steady state concentration of only 46.2% lactulose with an 88 min hold-up.

Multiple equal-sized backmix reactors (CSTRs) in series will give an effluent with a higher product concentration than a single CSTR of equal total volume. Conversion follows eqn (4).<sup>5</sup>

$$C_0/C_j = (1 + k_1\tau)_j \quad (4)$$

where  $j$  is the number of reactors in series.

Using two CSTRs in series ( $j = 2$ ) and assuming perfect mixing, at steady state, the conversion to lactulose would be 48.4% in the first CSTR and 65.6% in the second CSTR. Adding a plug flow reactor (2.6 dm<sup>3</sup> for this specific scale or throughput) after the two CSTRs should raise the conversion to 67.1% lactulose—not far from the 75% reached in a batch reactor.

This reactor process consisting of two CSTRs followed by a tubular reactor was investigated (Fig. 1) using a molar ratio of boric acid to lactose of 1.0 and a pH of 11.0. The goal was to determine the optimum operating parameters (temperature, time, agitation) and the steady state conversion. A series of runs was made at different temperatures to determine the best temperature. Figure 2 shows the conversion to lactulose increased until 71°C

and levelled off. There was no increase in conversion above 71°C. The best temperature found is 71°C.

Having established the temperature of 71°C, the effect of residence time in CSTR-A was studied. As shown in Fig. 3 conversion varied linearly with residence time. With a first order model, conversion is exponential. However, as conversion approaches the equilibrium level the curve approximates a line. The data for the plot in Fig. 3 are apparently near equilibrium and approximate a straight line. Conversion in CSTR-A and in reactor C increased with dwell time until about 44 min, after 44 min conversion appeared to drop off slightly, most likely due to the formation of by-products such as galactose and tagatose. Empirical eqns (5) and (6) give the approximate correlation for conversion to lactulose ( $ILS$ ) vs dwell time in CSTR-A and exit, C. The correlation coefficients were both 0.87.

$$ILS = 7.31(10^{-3})\tau + 0.26 \quad (5)$$

$$ILS = 4.26(10^{-3})\tau + 0.57 \quad (6)$$

The previous experiments were run with a reactor agitation rate in CSTR-A of 30–60 rpm and 240 rpm in CSTR-B. To study the effect of agitation, CSTR-A was agitated at 120 rpm and CSTR-B at 240 rpm which were convenient speeds to set for initial study. A recirculating centrifugal pump was installed after CSTR-B. By throttling this pump through a recycle to CSTR-B the flow rate out of reactor CSTR-B to reactor TR-C was controlled equal to the flow from CSTR-A to CSTR-B and greatly increased the agitation in CSTR-B. The average conversion for three runs was 74.7%. The recirculating pump was replaced with a Zenith metering pump. CSTR-A was agitated at 30–60 rpm and CSTR-B was agitated at 240 rpm. The average conversion for six runs was still 74.7%. Obviously, the recirculation in CSTR-B was unneeded.

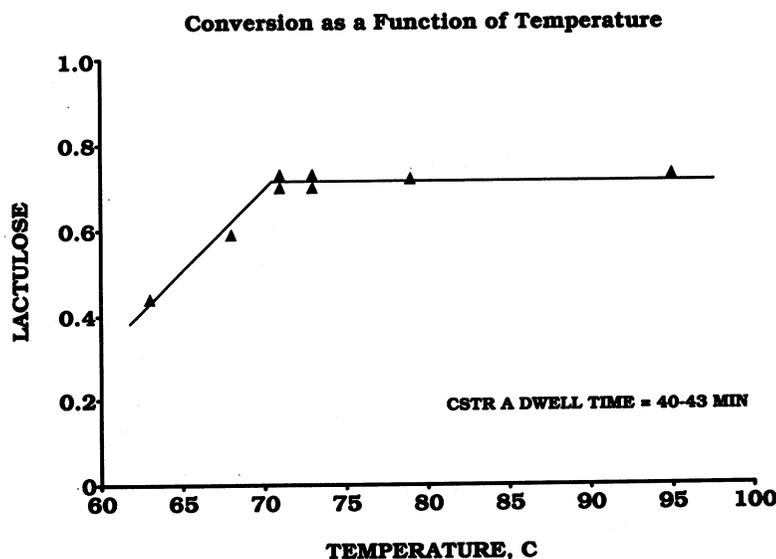


Fig. 2. Fractional conversion to lactulose in the reactor system as a function of reactor temperature in CSTR-A; pH = 11 and molar ratio boric acid/lactose = 1.

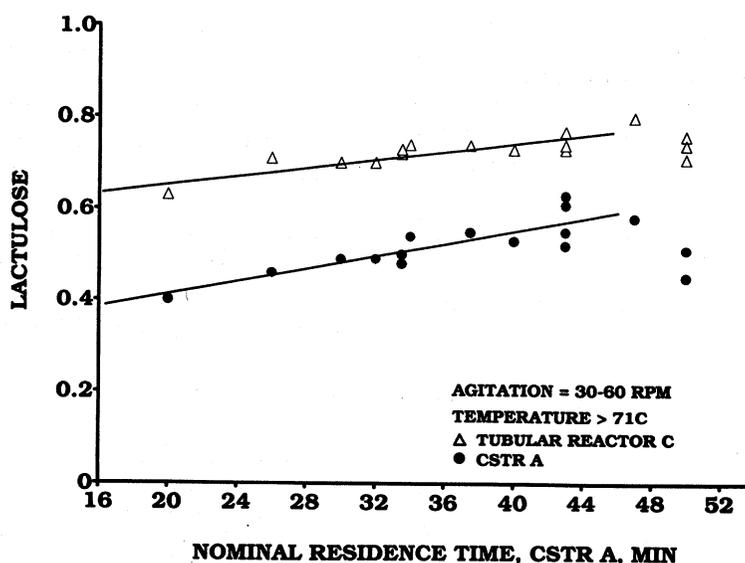


Fig. 3. Fractional conversion to lactulose in the reactor system (CSTR-A and TR-C shown) as a function of nominal residence time in CSTR-A; pH = 11 and molar ratio boric acid/lactose = 1.

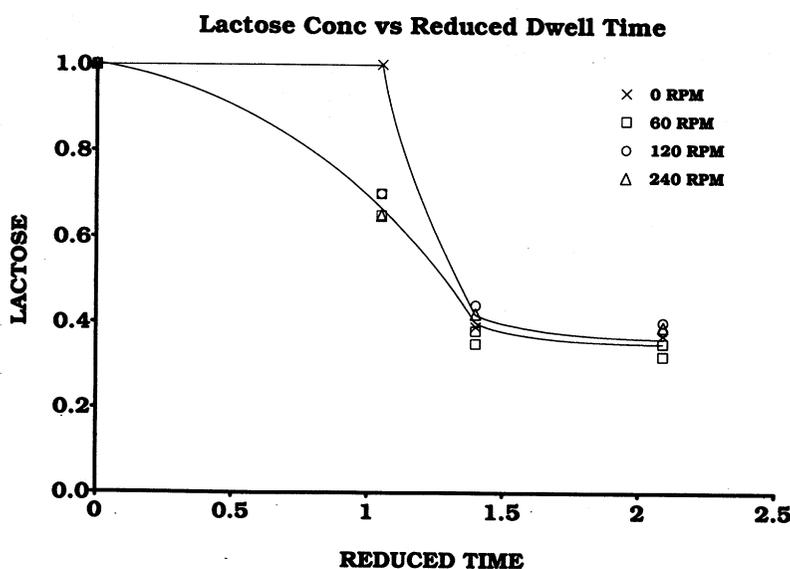


Fig. 4. Fractional conversion (loss) of lactose in CSTR-A as a function of reduced dwell time for no agitation and for agitation at 60–240 rpm; 71°C, pH = 11, and molar ratio/lactose = 1.

Holding the agitation in CSTR-B at 240 rpm, the effect of agitation in CSTR-A was studied. As shown in Fig. 4, with no agitation, there was a sudden drop in lactose concentration at a nominal reduced residence time of about 1.0 as observed in plug flow. The reactants may have layered on the surface of the reactant mixture. The phenomenon should be specific to this particular reactor. Unfortunately, it was impractical to run the reaction with no agitation since it resulted in very poor heat transfer.

A series of runs was made in which the agitation in CSTR-A was changed while maintaining a nominal 22.7 dm<sup>3</sup> in CSTR-A, 44 min residence time, and a temperature of 71°C. There was a slight drop in conversion with agitation with a maximum at about 30–60 rpm. An agitation rate of 30 rpm was chosen because it was the slowest, practical agitation rate above 0 rpm which could be maintained in CSTR-A.

To confirm that the reactor system and parameters chosen were practical for process development, a series of experiments was made at these conditions. Table 1 lists the results. A second set of experiments was made in which the solids concentration in the feed was increased to 20%. Table 1 also lists these results. The average conversion for the combined experiments was  $76.1 \pm 7.2\%$  at the 95% confidence interval. This is very close to the 75% conversion found in the laboratory level batch studies. The data suggest a slightly higher conversion using 20% solids feed concentration. A null hypothesis was made comparing the average conversion in each reactor at the different solids levels. The results indicate no statistically significant difference at the 95% confidence level in conversion from CSTR-A or CSTR-B but a significant difference in the conversion from TR-C. The average conversion with 10% solids was  $73.6 \pm 1.5\%$  and

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**TABLE 1**  
Lactulose Conversion Exiting Each Reactor

CSTR-A	CSTR-B	TR-C	% Solids
55	71	73	10
53	71	73	10
50	71	74	10
55	72	74	10
52	72	74	10
52	70	74	20
60	75	77	20
58	77	79	20
61	78	81	20
64	80	82	20
60	74	76	20

71–75°C; pH = 11.1–11.5; molar ratio boric acid/lactose = 1.04; 44 min nominal residence time in CSTRs; agitation in CSTR-A = 30 rpm.

78.2 ± 7.9% at the 20% solids level. This indicates it is best to run the reactors at the 20% solids level. A higher level is not practical due to insolubility of the lactose at higher levels.

## CONCLUSIONS

The reactor process chosen consisted of three reactors in series, two-equal sized backmix reactors (CSTRs) and a tubular reactor. The volumetric hold up in each CSTR was 22.7 dm<sup>3</sup> and in the tubular reactor was 2.6 dm<sup>3</sup>. Nominal residence time in each CSTR was 44 min at a flow rate of 0.53 dm min<sup>-1</sup>. Temperature was 71–75°C with agitation in the first CSTR at 30 rpm and in the second CSTR at a nominal 240 rpm.

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