Organic Process Research & Development **2009,** *13,* 629–633

Technical Notes

Hydrogenation of a Pharmaceutical Intermediate by a Continuous Stirred Tank Reactor System

John G. Van Alsten,* Matthew L. Jorgensen, and David J. am Ende

Engineering Technologies Laboratory, Pfizer Global R&D, Groton, Connecticut 06340

Abstract:

A proof of concept study on the continuous hydrogenation of a pharmaceutical intermediate is presented. A slurry feed of CP-548495, a dintro intermediate in a smoking cessation drug, was reduced in a two-reactor continuous stirred tank train to the diamine product. The reactors were found to operate within different kinetic regimes, with the upstream reactor exhibiting hydrogen mass transfer limited behavior, and the downstream reactor, substrate concentration limited behavior. A longer-term catalyst degradation study was conducted to explore the potential for extended operation.

Introduction

A significant amount of work has transpired regarding the potential of supplanting batch reactions and processes with continuous ones. One of the largest reaction classes is hydrogenations, which by one estimate constitute ~20% of all fine chemical synthetic reactions.[1] These steps appear particularly ripe for improvement by continuous technology for numerous reasons:

* Safety: Minimization of hydrogen inventory and smaller-diameter vessels for increased mechanical integrity under high pressure. A decreased need for manual catalyst handling, often considered the most hazardous of operations. More stable reaction control by operating under steady state.
* Quality: With smaller volumes, hydrogen mass transfer rates may be more tightly controlled, allowing the potential to minimize impurities due to either hydrogen starvation or over-reduction.
* Cost: The potential to increase catalyst utility from the current typical range of 20−100 kg product/kg catalyst to perhaps ~1000 kg/kg. The reduction of cycle times inherent in charging/purging/filtering operations. Reduced waste streams from catalysts and washes.

While the benefits appear significant, continuous operation of a three-phase (solid−liquid−gas) reactor system requires increased operational sophistication compared to the traditional batch reactor. A variety of configurations are available at commercial scale, including continuous stirred tank reactors (CSTR), venturi, fluidized bed, loop, and trickle bed reactors. Excellent reviews of the relative merits of these have been published.[2] Because a pharmaceutical processing facility must be capable of processing a wide variety of feeds under widely varying conditions, we contend that the CSTR or loop reactor is the most practical option. Since the smallest loop configuration requires a minimum of 15 L, its use for early phase process development is quite limited.[3] Hence, the CSTR is the most useful reactor configuration for relatively small scale development studies. Any catalyst currently in use in a stirred tank can be utilized in the CSTR, and batch kinetic data may be translated to a CSTR train with standard methods.[4] Wang has demonstrated a CSTR system in the homogeneous reduction of an intermediate in the synthesis of mibefradil.[5] We report here on extending this approach to heterogeneous (substrate slurry and solid catalyst) hydrogenation of an intermediate used for the manufacture of a drug for smoking cessation.

Chemistry. The reaction under consideration is the reduction of the aromatic nitro groups of CP-548495, an intermediate in the synthesis of varenicline, the active ingredient of Chantix (U.S.A) or Champix (EU). The commercial process for this material is a telescoped reduction of the dinitro intermediate to the diamine followed by cyclization with glyoxal and hydrolysis to form the API[6] (Scheme 1). Since considerable effort had already been expended in the optimization of the reaction conditions and because we sought to explore a continuous "drop-in" alternative for the current batch process, the study was constrained to conditions similar to those used commercially, which involve contacting hydrogen and about 3 wt % of 5% Pd/C with a 5% solution of substrate in a mixture of isopropanol/water until the reaction is complete. The product

* Author to whom correspondence may be sent. E-mail: john.g.vanalsten@pfizer.com.

(1) Doku, N.; Verboom, W.; Reinhoudt, D. N.; van den Berg, A. *Tetrahedron* **2005**, *61* (11), 2733.

(2) (a) Edvardsson, J.; Irandoust, S. *J. Am. Oil Chem. Soc.* **1994**, *71* (3), 235. (b) Jenk, J. F. In *Heterogeneous Catalysis and Fine Chemicals II*; Guisnet, M., Ed.; Elsevier Science Publishers: Dordrecht, The Netherlands, 1991. (c) Stitt, E. H. *Chem. Eng. J.* **2002**, (90), 47. (d) Patterson, H. B. W. *Hydrogenation of Fats and Oils: Theory and Practice*; American Oil Chemists' Society (AOCS Press): Champaign, IL, 1994. (e) Puri, P. S. *J. Am. Oil Chem. Soc.* **1980**, (November), 850A.

(3) Product literature and personal communications, BUSS ChemTech AG, Switzerland. .

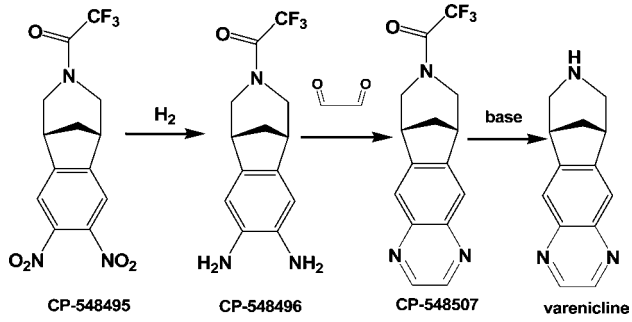
(4) (a) Levenspiel, O. *Chemical Reaction Engineering*; John Wiley & Sons: New York, 1999. (b) Murthy, A. K. S. *Chem. Eng.* **1999**, *106* (10), 94.

(5) Wang, S.; Kienzle, F. *Org. Process Res. Dev.* **1998**, *2* (4), 226.

(6) Busch, F. R.; Hawkins, J. M.; Mustakis, L. G.; Sinay, T. G.; Watson, T. J. N. Preparation of High Purity Substituted Quinoxaline. WO/2006/090236 A1, 2006.

10.1021/op800170r CCC: $40.75
Published on Web 02/04/2009

Scheme 1. **Synthetic sequence to varenicline**



of the reduction is not isolated from solution but is taken as is to the cyclization. The yield over these three steps is ~80%.

The hydrogenation of aromatic nitro groups is the subject of an enormous body of literature.[7] The particular reaction pathway appears to be dependent on the precise reaction conditions, e.g., catalyst, temperature, and substrate concentration. In the hydrogenation of neat aniline, for example, appreciable quantities of azobenzene and azoxybenzene are formed.[8] Kinetic experiments clearly show that in our system the material undergoes at least three separate adsorption/reduction steps on the path to complete reaction, as the nitroso/nitro, nitroso/hydroxylamine, and diamine are all identified in the reactor supernatants (Scheme 2). Analysis of process streams allows us to quantify conversion in terms of the number of equivalents of hydrogen by:

$$\text{Conversion} = \frac{[NO/NO_2] + 3[NH_2/NO_2] + 6[NH_2/NH_2]}{6} \quad (1)$$

CP-548495 is a compound with a high thermal potential but a reasonably high onset temperature near 230 °C. The adiabatic temperature rise of the hydrogenation reaction is 57 °C so that even under these conditions there is little decomposition hazard from the starting material. The properties of the intermediates are unknown, however, although hydroxylamines are known to be relatively unstable materials. One of the advantages to a continuous reactor is that it operates at steady state, with reaction rate and heat evolution controlled by the rate at which reactants are fed to the reactor. Hence, there is no exotherm per se in an ideal continuous reactor. It will also be demonstrated that the system operates in a regime where the concentration of intermediates is low, further reducing the risk of an undesirable decomposition event.

Reactor System. The reaction system (Figure 1) consists of two 0.1 L stirred, jacketed vessels with inlets and outlets for feeds, products, and sampling. The reactors are constructed of Hastelloy C and are 8.9 cm tall and 4.1 cm in diameter. Small removable baffles may be inserted into the vessels, onto which may be attached fixed catalyst beds constructed of fine wire mesh. The impeller is a six-bladed vortexing system that is designed to push fluid radially outward through the fixed catalyst beds. Substrate may be fed either as a solution via HPLC pump

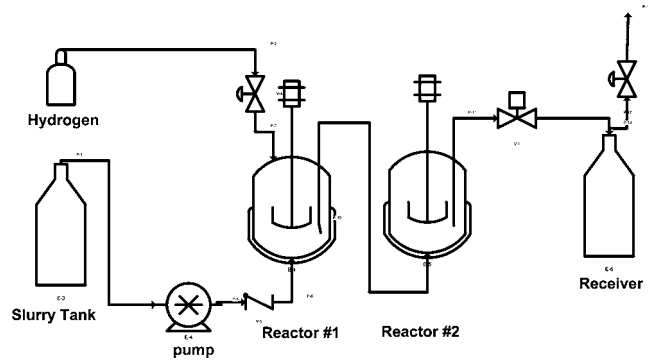
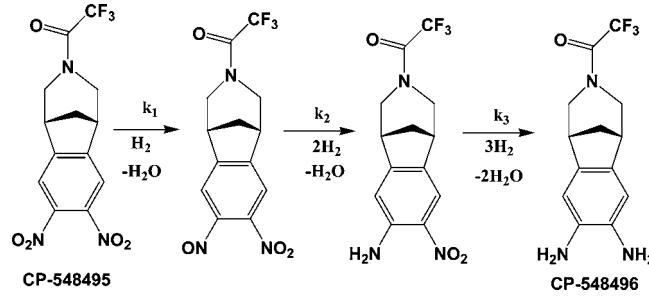


Figure 1. **CSTR hydrogenation system. Substrate slurry and hydrogen are fed to reactors with fixed catalyst beds. Level is maintained by dip tube. Slug flow of product liquid and excess gas is reduced to near atmospheric pressure over a control valve.**

Scheme 2. **Reduction of the CP-548495 showing identified intermediates**



(Laboratory Alliance Series III) or as a slurry via diaphragm pump (Prominent gamma2L), with a check valve to restrict backflow. Hydrogen gas is introduced into reactor #1 via mass flow controller (Brooks) and serves as both reactant and source of hydrostatic head to drive the product solution downstream. From reactor #2 the process stream flows across a control valve (Badger Meter, Inc., Tulsa, OK, U.S.A.) and into a nitrogen-purged receiver vessel where excess gas is vented. While operationally simple, the use of hydrogen as the fluid "pump" prevents accurate quantification of gas uptake. The system was constructed by Pressure Products Industries (Warminster, PA, U.S.A.) and instrumented by Crest Integrators (Erie, PA, U.S.A.). The reaction residence time is controlled by manipulating liquid feed rate and the reaction volume, the latter determined by level control of the reactors and set by the height of a stand pipe. The most significant challenge is the need to confine the catalyst within the reactor volume while removing the product-containing liquid stream. In larger-scale commercial operations this is often handled in a dedicated external crossflow filtration unit,[9] which unfortunately, is not practical on the small laboratory demonstration scale. Instead, we have chosen to either confine the catalysts to a flow-through bed located annularly within the reactor or utilize *in situ* crossflow filters. Neither approach is without compromise, i.e., reduced catalyst activity for the former or eventual filter blinding by the latter. In this contribution we present results only from the use of fixed flow-through beds.

(7) (a) Rylander, P. N. *Hydrogenation Methods*; Academic Press: New York, 1985. (b) Visentin, F.; Puxty, G.; Kut, O. M.; Hungerbuhler, K. *Ind. Eng. Chem. Res.* **2006**, *45*, 4544.

(8) Wisniak, J.; Klein, M. *Ind. Eng. Prod. Res. Dev.* **1984**, *23*, 44.

(9) *Catalyst Recovery from Continuous Flow Reactors with Mott Hypulse® LSM Filters*, technical publication. Mott Corporation: Connecticutt, U.S.A., 1997.

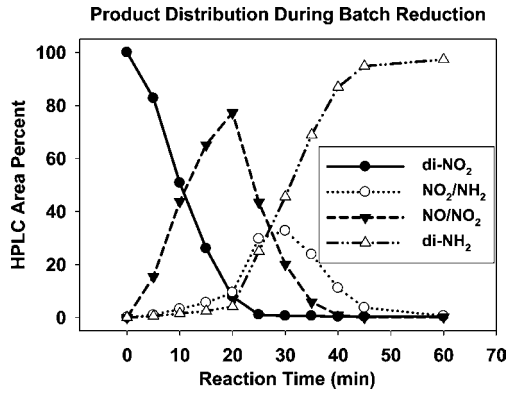


Figure 2. **Distribution of intermediates during batch reduction. Granular catalyst.**

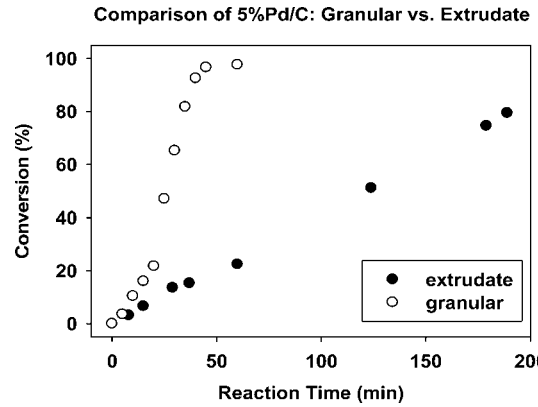


Figure 3. **Batch kinetic experiments contrasting performance of two morphologies of 5% Pd/C.**

We have found that one of the highest barriers to effective laboratory *scale down* is in handling slurries, where the low momentum inherent with small flow rates makes solids fluidization difficult at best. The study presented here required a feed of reactant slurry to a reactor under a modest (5.2 barg) head of hydrogen. To effect this we first wet milled the reactant to reduce its particle size from ~250 to 50 μm. This allowed particle fluidization in a stirred feed tank sufficient to be successfully injected into the reactor using the high-pressure diaphragm pump (Prominent gamma/2 L).

Catalyst Selection. All reactions described herein were performed under a hydrogen pressure of 5 barg and a temperature of 50 °C. The two catalysts screened were 5% Pd on carbon support, and were obtained in very different morphologies. One support was extruded carbon pellets of dimensions ~2 mm in diameter and 5 mm in length (Englehard Corp., SOC10161). The second was a granular carbon with randomly shaped particles ranging from 5 to 30 μm in size (Englehard Corp., CD04063). These were retained within the reactors by sealing within metal mesh, which was then fixed to the thermowells and baffles within the reactors. Smaller catalyst particles common to batch processing were not investigated because of our inability to retain them in a mesh large enough to allow unrestricted liquid flow. Batch screening tests demonstrated a profound difference in activity of the two materials, with the granular material being ~3−4× more active than the extrudate. In each case two reaction intermediates are observable by HPLC. (Figure 2) The granular material exhibits kinetics indicative of both hydrogen-limited and substrate-limited regimes with conversion essentially linear with time up to ~90%, indicative of a regime limited by the mass transfer of hydrogen into the solution. (Figure 3) Beyond this level, conversion slows as substrate concentration diminishes. All further experimentation was conducted exclusively with the granular catalyst.

Experimental Section

Hydrogen (Airgas UHP, 99.999%) was supplied by tank. CP548495 was supplied by Pfizer Global Manufacturing and used as received. Isopropanol was laboratory grade, and water was from the tap.

About 1.25 L of feed was prepared by charging 60 g of CP548495 and 1.2 L of 80/20 isopropanol/water mixture to a vessel equipped with an overhead homogenizer (IKA T-25) and homogenizing for ~2 h. To begin a run, 1.3 g of catalyst was loaded into each of two screened containers which were attached to the removable baffle for each vessel. The reactors were then installed in the system. Reactor #1 was isolated from downstream by closing a valve, and then 50 mL of reactant slurry was injected into it; 50 mL of solvent was charged by syringe to reactor #2. The system was purged of air by five pressurization/vent cycles with 0.7 barg nitrogen, and heated to 50 °C. Five pressurization/vent cycles of hydrogen at 5.2 barg were then performed, and agitation commenced. The reaction was sampled for completion after ~1 h and the feed of CP-548495 slurry begun at a rate of 0.36 mL/min. (A residence time of 140 min.) The isolation valve was opened to allow material flow to reactor #2. After about ten more minutes, the outlet valve was opened to enable product and excess hydrogen to exit into the receiver, which was mounted on a weigh scale. Samples of the reactors' contents were collected periodically via needle valves at the bottom of each vessel. The system was operated in continuous mode for about 10 h. Material from the reduction was not taken on to an isolated product.

Physically, the reaction proceeds from a 20 L/kg slurry in a mixture of 80/20 isopropanol/water and becomes a solution at a conversion of CP-548495 of about 70%. As our small flow rates preclude transport of slurry from reactor to reactor, this fixes the minimum residence time in the vessel to about 50 min, or an overall residence time of 100 min.

Samples were analyzed by HPLC (Agilent) using a C18 column and an acetonitrile/water (0.1% formic acid) gradient, with detection at 230 nm. HPLC/MS (Agilent) was performed on selected samples for intermediate identification. Assignments were made by the presence of the molecular ion in each case. In the case of the nitroamine, which has a mass identical to that of the nitroso/hydroxlamine, identification was further refined by the absence of an M-30 (NO) peak that was observed in high intensity in the spectrum of the nitroso/nitro species.

Results

Measured over time on stream, the concentrations of the intermediates are sensitive indicators of the attainment of steady state and the natural fluctuations inherent in the system. Figure 4 illustrates that the relative product distribution in reactor #1 fluctuates by as by as much as 7% in terms of residual dinitro material. Extension of the batch reactor behavior shows that

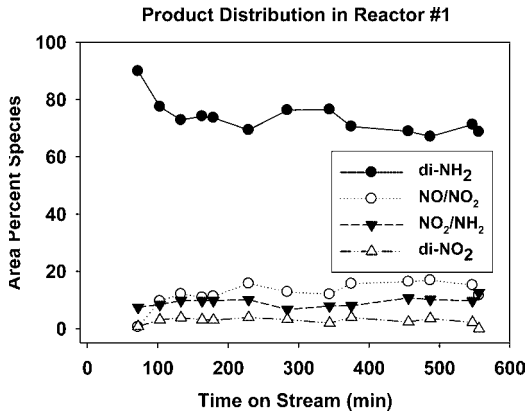


Figure 4. **Product distribution in reactor #1 measured during time of operation.**

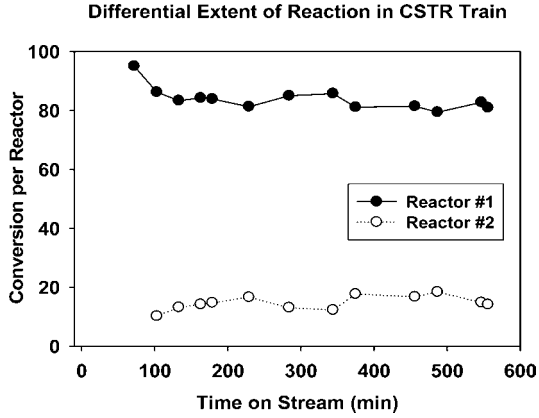


Figure 5. **Differential conversion in each reactor over time of operation.**

reactor #1 operates exclusively within the kinetic regime limited by hydrogen mass transfer. Overall conversion also fluctuates in reactor #1 by about 6% beyond startup (Figure 5). While we have not isolated the cause of these fluctuations, two sources appear likely. The first might be due to slight variations in the charge of slurry delivered by the diaphragm pump. The second might be caused by the variations in the reactor residence time caused by the slug flow nature of our system, which forces the reactor level to alternate between the level of the dip pipe to slightly overfilled. Regardless of these fluctuations, comparison with Figure 3 indicates that this reactor is operating in the kinetic regime limited by hydrogen mass transfer.

The main function of the downstream reactor is to carry the reaction to completion. In contrast to reactor #1, reactor #2 operates in the kinetic regime limited by substrate concentration. Figure 5 shows that the rate of reaction is on average only 18% of that in the first reactor. There is also an inverse correspondence in reaction rate between reactors # 1 and #2: when conversion in #1 is highest, the reaction rate in #2 is relatively low, and when conversion in #1 dips, the rate in #2 increases. (Figure 6) Thus, reactor #2 automatically compensates for fluctuations in the performance of the first reactor. As a result, the total variation in outlet composition of the reactor train at steady state is quite small, ranging from 97.4 to 98.6% CP-548496 (Figure 7).

Two of the most difficult questions to address for bench-scale laboratory evaluation of continuous processes are (1) achievement of steady state in the system and (2) evaluating viability of extended

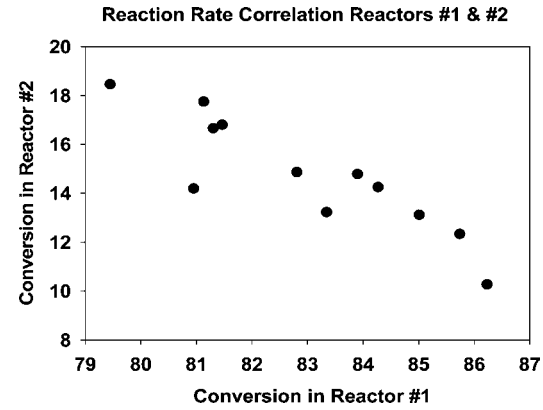


Figure 6. **Correlation of reaction rate between reactors, showing how reactor #2 compensates for fluctuation in conversion from reactor #1.**

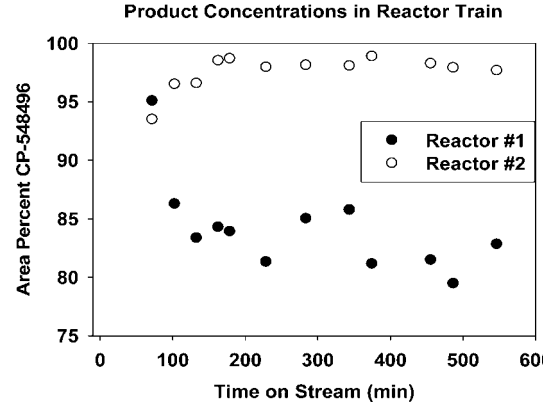


Figure 7. **Outlet product compositions of both reactors measured over time of operation.**

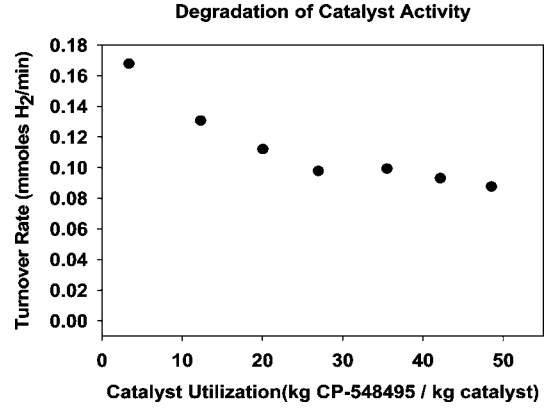


Figure 8. **Measurement of catalyst activity as a function of the mass of CP-548495 processed.**

operation that might be on stream for days, weeks, or months. In most real catalysis the temporal degradation of catalyst activity makes establishment of a truly steady state impossible and eventually limits the total quantity of material processable. Due to time limitations, the total catalyst utility of the work presented here is still rather low at 7 kg substrate/kg catalyst, significantly lower than the 20−30 kg/kg typical of batch hydrogenations in our industry. To investigate further the possible long-term impact of activity degradation, a series of batch experiments was performed in which we recycled catalyst to fresh feeds and deliberately ran to incomplete conversions. Figure 8 shows that catalyst activity undergoes a marked decrease in the early cycles before plateauing (or with a mild rate of decrease) near about 30 kg/kg. For long-

term operation it is apparent that the processing rate would thus be about 50−60% of that demonstrated in our short duration run. Conversely, this could be ameliorated by approximately doubling the catalyst charge.

The work presented here represents the initial steps on a long path to commercialization. A significant body of engineering work on catalyst handling, long-term stability, startup, shutdown, and a myriad of other issues remains to be addressed. These issues are balanced somewhat by the fact that many of the problems inherent in laboratory scale down are more readily resolved when moving to larger scale facilities. For example, operational difficulties with transport of slurries, feed control, and level control are much less problematic at large scale. We thus submit that the CSTR platform represents an attractive and potentially quite practical commercial alternative to batch processing.

Conclusions

We have presented a proof of concept study on the potential for continuous hydrogenation of pharmaceutical intermediates. A laboratory CSTR system utilizing a slurry feed of substrate in solvent was run for ∼10 h to demonstrate the feasibility of this approach. While significant work is still required for commercialization, we believe that many of the engineering difficulties inherent in small-scale operation will diminish on scale-up.

Received for review July 21, 2008.

OP800170R