Organic Process Research & Development **2009,** *13,* 1080–1087

Evaluation and Establishment of a Cleaning Protocol for the Production of Vanisal Sodium and Aspirin Using a Continuous Oscillatory Baffled Reactor

Caldeira Ricardo and Ni Xiongwei*

Centre for Oscillatory Baffled Reactor Application (COBRA), School of Engineering and Physical Sciences, Heriot-Watt University, Edinburgh EH14 4AS, U.K.

Abstract:

The robustness and adaptability of a continuous oscillatory baffled reactor (COBR) in organic syntheses of vanisal sodium and aspirin were tested whilst meeting the stringent regulatory standards. In one week-long continuous operation, vanisal sodium was produced to a purity level of 99.94%, aspirin to a level of 99.57%. The loss of product during the cleaning process amounted to 0.001% and 0.005% for vanisal sodium and aspirin, respectively. The data of the continuous syntheses show that the operation of the COBR is robust and consistent throughout the week-long period. The cleaning stage that was used after each production campaign exhibited a first-order kinetics and was effective and efficient.

Introduction

Continuous manufacturing has been identified as one of the key elements in improving manufacturing in the chemical and pharmaceutical industries, through more efficient use of reagents, solvents, energy, and space whilst minimizing the production of waste materials and reactor downtime for reactor maintenance and cleaning.[1−6] In order to become a viable alternative to traditional batch stirred tank reactors, continuous reactors must operate consistently and must be easy to clean and adaptable to different manufacturing processes while minimizing the risk of cross-contamination.[7,8]

It is challenging for a new continuous technology to penetrate into the increasingly cautious world of the aforementioned industries, even more so if it entails a paradigm shift in the long-established manufacturing processes. Proactive companies that are prepared to engage in a proven yet emerging technology earlier than their rivals gain a competitive advantage.[9,10] However, the process of exploring novel technologies often remains confidential, in terms of the adoption of a new technology by its potential users, research done behind closed doors needs to be published to be legitimized.[4,11]

When chemical and pharmaceutical companies consider using a continuous reactor technology for a given process they expect not only similar or better levels of adaptability and flexibility compared to its traditional counterpart, but also look for simplicity and effectiveness of the cleaning procedure to minimize the degree of cross contamination when the manufacture of different products is undertaken.

It is well-known that the cleaning process in the chemical and pharmaceutical manufacturing industries is traditionally empirical and case specific.[12] Cleaning conventional mixers usually involves down-time and off-line washing of the reactor and parts, lengthening the turnaround time and increasing waste and costs.[13] In terms of containment, cleaning can in itself be another source of contamination, since these cleaning procedures are typically done while the vessel is in contact with the outside environment.[14] In order to meet the increased stringency concerning the purity of produced active pharmaceutical ingredients (APIs) and other chemicals required by regulating agencies around the world, there is a current drive towards better cleaning standards and practices that are cost-effective and at the same time reduce waste, reactor downtime and costs.

It is within this context that this work, funded by the Engineering and Physical Sciences Research Council (EPSRC) through the Chemistry Innovation Knowledge Transfer Network (CIKTN), UK and NiTech Solutions Ltd., a SME based in Glasgow, Scotland, was carried out. This paper reports the experimental studies of using a continuous oscillatory baffled reactor (COBR) for the production of two important products:

* Corresponding author. Telephone: 0044 131 451 3781. FAX: 0044 131 451 3129. E-mail: email: x.ni@hw.ac.uk.

(1) Pellek, A.; Arnum, P. V. Continuous Processing: Moving with or against the Manufacturing Flow. *Pharm. Technol.* **2008**, *32* (9), 52–58.
(2) Swichtenberg, B. Moving Beyond the Batch. *Pharm. Manufact.* **2008**, *7* (1), 24–26.
(3) Vervaet, C.; Remon, J. P. Continuous granulation in the pharmaceutical industry. *Chem. Eng. Sci.* **2005**, *60* (14), 3949–3957.
(4) Gron, H.; Mougin, P.; Thomas, A.; White, G.; Wilkinson, D. Dynamic In-Process Examination of Particle Size and Crystallographic Form under Defined Conditions of Reactant Supersaturation as Associated with the Batch Crystallisation of Monosodium Glutamate from Aqueous Solution. *Ind. Eng. Chem. Res.* **2003**, *42*, 4888–4898.
(5) Liu, D. H. F.; Lipták, B. G.; Bouis, P. A., Eds. *Environmental Engineers' Handbook*, 2nd ed.; Lewis Publishers, Inc.: Boca Raton, FL, 1997.
(6) Crosby, T. Designing For the Future of Continuous Processing. *Pharm. Process.* **2006**, *22* (1); http://www.pharmpro.com/ShowPR.aspx?PUBCODE=021&ACCT=0000100&ISSUE=0601&RELTYPE=PR&Cat=0&SubCat=0&ProdCode=0000&PRODLETT=A&SearchText=crosby (accessed Oct 5, 2009).
(7) Angelucci, L. A. I. Current Good Manufacturing Practice Design Trends In Active Pharmaceutical Ingredients Facilities. *Drug Inf. J.* **1999**, *33*, 739–746.
(8) Plumb, K. *Continuous Processing in the Pharmaceutical Industry: Changing the Mind Set Chemical Engineering Research and Design* **2005**, *83* (6), 730–738.
(9) Scarso, E. Timing the adoption of a new technology: An option-based approach. *Manage. Decis.* **1996**, *34* (3), 41–48.
(10) Rios, M. Continuous Processing - Finally. *Pharm. Technol.* **2007**, *31* (4), 64–67.
(11) By Do-Coop Technologies. Playing ball with the Pharma 'Big Boys'. *Next Generation Pharmaceutical Europe* **2008** (6); http://www.ngpharma.eu.com/article/Playing-ball-with-the-Pharma-Big-Boys/ (accessed Oct 5, 2009).
(12) Perka, A. T.; Grant, C. S.; Overcash, M. R. Waste minimization in batch vessel cleaning. *Chem. Eng. Commun.* **1993**, *119* (1), 167–177.
(13) Chew, J. W.; Shan, P. S.; Tan, R. B. H. Automated in-line technique using FBRM to achieve consistent product quality in cooling crystallization. *Cryst. Growth Des.* **2007**, *7* (8), 1416–1422.
(14) Gambrill, J. S. *Apparatus and method for in-place cleaning of a mixer*. U.S. Patent 5,427,450, 1995.

10.1021/op900120h CCC: $40.75
Published on Web 10/06/2009

vanisal sodium (a chemical) and aspirin (a pharmaceutical), in sequence on the same machine. Each reaction was run for 7 days, 24 h a day, interspersed by a cleaning stage.

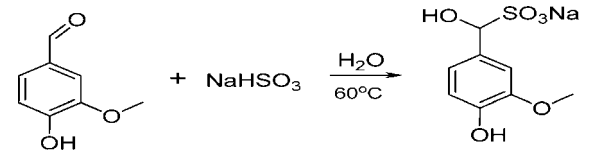
A COBR is a mixing/reaction device consisting of a tube with periodically spaced orifice baffles, perpendicularly orientated in relation to the flow. The flow inside the tube is superimposed with oscillatory motion, caused by a motor placed at one or both ends of the reactor. Disruption of the flow occurs when the fluid encounters a sharp restriction and eddies around the annular baffles are formed.[15,16] This continuous generation and cessation of eddies provides a vigorous axial and radial mixing in the reactor.[17,18] Each baffled cell can be considered as a perfectly mixed continuous stirred tank reactor (CSTR); as a consequence of this the entire COBR behaves as a large number of perfectly mixed CSTRs in series. Very sharp residence time distributions, i.e. plug-flow characteristics, are achieved using this reactor technology.[19]

Extensive studies using the COBR demonstrate that its characteristics allow for a significant improvement in mixing and heat[20] and mass transfer rates.[21] This reactor design has shown success when tested for several industry-relevant processes, such as mixing and particle suspension,[22] polymerization,[23] fermentation,[24] crystallization,[25] photooxidation,[26] and biodiesel production,[27] just to name but a few.

Although there are industrial COBRs in use,[28] there are currently no published data on the robustness and reliability of this reactor design for long periods of operation, no data on continuous multiproduct manufacturing or on cross-contamination matters when a single COBR is employed to produce different chemical entities, testing its manufacturing versatility. This was the first study of its kind.

Experimental Section

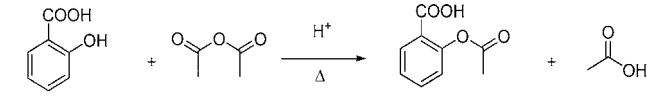
Reaction Schemes. *Vanisal Sodium.* Vanillin is the molecule that is normally used to evoke the smell of vanilla and that is relatively stable in perfumes but not in soap formulations. Due to the combination of light, heat, and basic conditions in soaps, vanillin and its derivatives undergo chemical reactions that rapidly transform them into polyphenols and other detergent products. The outcome of these events is the discoloration of soaps, from a light tone progressively to darker brown and eventually black, as well as the loss of foaming power.[29,30] Vanisal sodium, the product of the treatment of vanillin with a sulfiting agent, is the solution to this problem: it does not suffer from discoloration when used in the composition of soaps and retains the much appreciated vanilla scent.[30] The reaction scheme for the production of vanisal sodium is shown below; it is a second-order reaction:



vanillin vanisal sodium

The experimental procedure is the following: vanillin and water were mixed in a batch oscillatory baffled reactor (OBR) that was preheated to 60 °C. Sodium hydrogen sulfite (40% w/w) and the mixture were then separately fed into the COBR, which was also heated and maintained at 60 °C. The COBR was operated at laminar flow condition throughout the campaign. Samples were taken every six hours. In this synthesis, a constant temperature of 60 °C was used throughout the COBR.

Aspirin. More than a century after the Bayer pharmaceutical company started selling aspirin, acetylsalicylic acid is still one of the most widely used over-the-counter drugs in the world. Nowadays, over 35,000 tons are produced and consumed annually, the equivalent to ~100 billion tablets.[31] The synthesis of acetylsalicylic acid involves the acetylation of salicylic acid by acetic anhydride in an acidic medium as shown below and is again a second-order reaction:



salicilic acid acetic anhydride acetylsalicylic acid acetic acid

(15) Brunold, C. R.; Hunns, J. C. B.; Mackley, M. R.; Thompson, J. W. Experimental observations on flow patterns and energy losses for oscillatory flow in ducts containing sharp edges. *Chem. Eng. Sci.* **1989**, *44*, 1227–1244.

(16) Sommer de Gelicourt, Y. On single phase axial dispersion in oscillatory baffled columns. M.Phil. thesis, Heriot-Watt University, Edinburgh, U.K., 2000.

(17) Nelson, G. A scale up study in suspension polymerisation of methylmethacrylate in a pilot oscillatory baffled reactor. Ph.D. Thesis, Heriot-Watt University: Edinburgh, U.K., http://worldcat.org/oclc/53608706, 2001.

(18) Mackley, M. R.; Ni, X.-W. Mixing and dispersion in a baffled tube for steady laminar and pulsatile flow. *Chem. Eng. Sci.* **1991**, *46* (12), 3139–3151.

(19) Ni, X.; Pereira, N. E. Parameters affecting fluid dispersion in a continuous oscillatory baffled tube. *Am. Inst. Chem. Eng. J.* **2000**, *46* (1), 37–45.

(20) Mackley, M. R.; Tweedle, G. M.; Wyatt, I. D. Experimental heat transfer measurements for pulsatile flow in baffled tubes. *Chem. Eng. Sci.* **1990**, *45* (5), 1237–1242.

(21) Hewgill, M. R.; Mackley, M. R.; Pandit, A. B.; Pannu, S. S. Enhancement of gas-liquid mass transfer using oscillatory flow in a baffled tube. *Chem. Eng. Sci.* **1993**, *48* (4), 799–809.

(22) Liu, S.; Ni, X.; Greated, C. A.; Fryer, P. J. Measurements of velocities of single particles for steady and oscillatory flows in plain and baffled tubes. *Trans. Inst.Chem. Eng.* **1995**, *73* (A), 727–732.

(23) Ni, X.; Zhang, Y.; Mustafa, I. Correction of Polymer Particle Size with Droplet Size in Suspension Polymerisation of Methylmethacrylate in a Batch Oscillatory Baffled Reactor. *Chem. Eng. Sci.* **1999**, *54*, 841–850.

(24) Gaidhani, H. K.; McNeil, B.; Ni, X. Production of pullulan using an oscillatory baffled bioreactor. *J. Chem. Technol. Biotechnol.* **2003**, *78*, 260–264.

(25) Ni, X.-W.; Liao, A. Effects of Cooling Rate and Solution Concentration on Solution Crystallization of L-Glutamic Acid in an Oscillatory Baffled Crystallizer. *Cryst. Growth Des.* **2008**, *8* (8), 2875–2881.

(26) Gao, P.; Ching, W. H.; Herrmann, M.; Chan, C. K.; Yue, P. L. Photooxidation of a model pollutant in an oscillatory flow reactor with baffles. *Chem. Eng. Sci.* **2002**, *58* (3−6), 1013–1020.

(27) Ni, X.; Mackley, M. R.; Harvey, A. P.; Stonestreet, P.; Baird, M. H. I.; Rama Rao, N. V. Mixing through oscillations and pulsations: A guide to achieving process enhancements in the chemical and process industries. *Trans. Inst. Chem. Eng.* **2003**, *81* (A), 373–383.

(28) Laird, I., Nitech - The Company. PI Meeting, Grangemouth, U.K., April 26, 2007.

(29) Vidal, J.-P. Vanillin. In *Kirk-Othmer Encyclopedia of Chemical Technology*; Kroschwitz, J., Ed.; John Wiley & Sons: Hoboken, NJ, 2006.

(30) Turin, L. *Color-stabilization of Aromachemicals.* WO/2007/013901, 2007.

(31) Classon, R. Spring Investor Conference (Bayer Healthcare), Leverkusen, Germany, March 18−19, 2004, *Safe Harbor*; Bayer AG: Leverkusen, Germany, 2004.

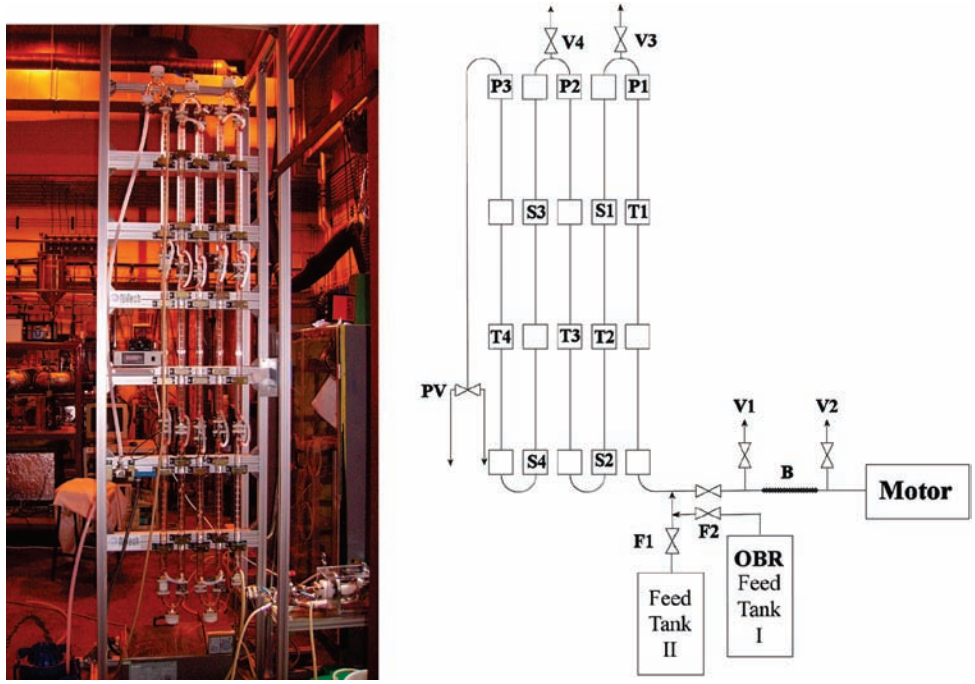


Figure 1. **(a) Photo of COBR. (b) Schematic of the COBR (B - bellow; F1 and F2 - feed valves; P1 to P3 - pressure gauges; PV - product 3-way valve; S1 to S4 - sampling valves; T1 to T4 - thermocouples; V1 to V4 - purge valves. V3 was removed to perform swab tests).**

The experimental procedure is the following: acetic anhydride and salicylic acid were mixed in a feed OBR that was preheated to 90 °C. The contents of the feed OBR as well as sulphuric acid (95% concentration) at room temperature were pumped individually to the COBR, which had the first four sections heated up to 60 °C. The cooling crystallization took place along the remaining 11 out of a total 15 glass baffled pipe sections of the COBR. Once again, the COBR was operated at laminar flow conditions throughout the test, and samples were taken at an interval of 6 h. In this process, variable-temperature profiles were required along the COBR.

Reactor. Figure 1a is a photo of the COBR; Figure 1b is a schematic representation of the setup. The COBR was purposely built by NiTech Solutions Ltd., and was made of a jacketed glass tube (15 mm in diameter) with perfluoroalkoxy (PFA) baffles. Each baffle was 3 mm thick with a restriction ratio of about 21%. The straight sections were connected by insulated glass U-bends, sealed with PTFE o-rings. The total length of the COBR was about 12 m, giving a total volume of about 2 L. There were four K-class thermocouple probes (T1 to T4) and three pressure gauges (P1 to P3) positioned along the COBR, as shown in Figure 1b. Two Watson-Marlow peristaltic pumps were used to deliver reactants to the system, and the oscillation was provided via a Parvalux rotary motor. Two 28 L water baths provided the heating/cooling fluids to the jacket of the COBR. A jacketed 1 L batch oscillatory baffled reactor (OBR) was used to prepare one of the feeds, while another container was employed for the supply of the additional reactant.

For each reaction studied the COBR was operated continuously without interruptions for seven days. Samples were taken regularly from the sampling ports along the length of the COBR (S1 to S4 in Figure 1b). In addition, swab samples were also taken at the location of V3. These samples were quenched immediately and analysed using high performance liquid chromatograph (HPLC) or nuclear magnetic resonance (NMR) spectroscopy for purity; scanning electron microscopy (SEM) and X-ray diffractometry (XRD) for crystal morphology.

Analytical Tools and Methods. HPLC: a Varian Prostar 230 chromatograph was used for the HPLC analysis, and the method utilized is an adaptation of a previously reported method.[32] The chromatography column is a reverse-phase YMC ODS-AQ (250 mm × 4.6 mm; 5 μm packing), the UV detector set at 254 nm and the mobile phase is composed by acetonitrile (A) and water with phosphoric acid at pH 2.6 (B). In each run the chromatography program is started with 10% of A and 90% of B, with a flow rate of 1 mL min^{-1}. The mobile phase composition is then gradually changed to 100% of A over a period of 20 min, and the program stops at 25 min. This method was developed so that optimal separations among vanillin, vanisal sodium, salicylic acid, and acetylsalicylic acid peaks were achieved.

NMR: The industrial manufacturer of vanisal sodium, Flexitral, employs NMR for determination of the purity of the product. Consequently we opted to use the same analytic tool in order for a comparison to be made. The equipment used was a Bruker DPX400 NMR spectrometer (^{13}C at 100 MHz) with pulsed field gradients.

SEM: Acetylsalicylic acid crystals were imaged using a Hitachi S-2700 Microscope. The gold coated crystals were observed at an amplification of 200×, using 10 kV accelerating voltage.

XRD: A Bruker D8Discover transmission X-ray diffractometer was used to examine the crystal structure of the produced aspirin. The data was obtained using WAXS.

(32) Franeta, J.; Agbaba, A.; Eric, S.; Pavkov, S.; Aleksic, M.; Vladimirov, S. HPLC Assay of acetylsalicylic acid, paracetamol, caffeine and phenobarbital in tablets. *Farmaco* **2002**, *57*, 709–713.

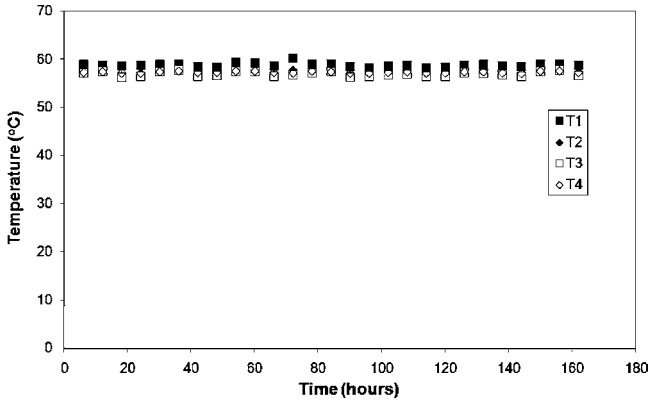


Figure 2. **Temperature measurements during the vanisal sodium reaction.**

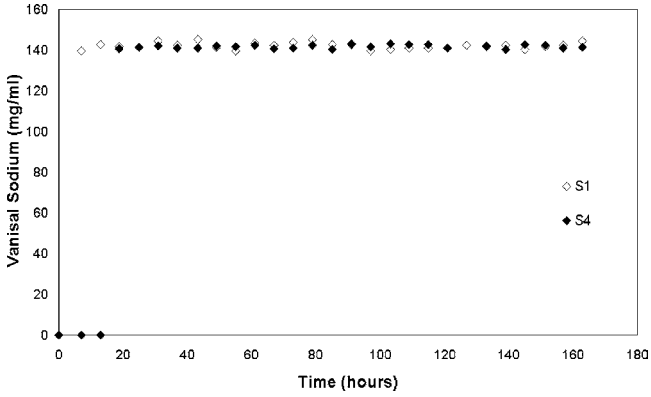


Figure 3. **Vanisal sodium produced continuously in the COBR.**

Materials. All the reactants used in the experimental runs were purchased from Sigma-Aldrich (Seelze, Germany). The USP grade water was acquired from VWR International (Lutherworth, England) and the Liquinox Solujet detergent (a mild anionic low-foaming phosphate free detergent) from Cole-Parmer (London, UK).

Results and Discussion

Vanisal Sodium. The temperature measurements from the four thermocouples (T1−T4) during the reaction are shown in Figure 2, and constant temperatures are seen along the COBR. This indicates that the environment within the COBR is highly consistent and reliable for the reaction. Samples were taken regularly at all four sampling ports (S1−S4), analysed and the amount of vanisal sodium produced was plotted against time. Figure 3 displays the data from sample locations S1 and S4 along the COBR. It is visible that there is a time delay in the product at the start from the furthest sample port in comparison to that at the closest location from the feed line, and the production of vanisal sodium was consistent during the whole the operation.

The purity of the product (vanisal sodium) using both NMR spectroscopy and HPLC was assessed; respective values were 99.92% and 99.95%. This indicates the consistency of both analytical methods, and the averaged purity was 99.94% over 54 samples.

The cleaning of the COBR started after the production run has been completed. A single-path cleaning-in-place (CIP) procedure was chosen. This is a common practice in the chemical and pharmaceutical industries and is critical to eliminate cross-contamination. In this protocol a fresh cleaning solution is fed to the reactor and then drained, and there is no residual circulation in the cleaning system.[33] As this was the first time that the cleaning process and procedure in a COBR were reported, we introduce two dimensionless groups that are relevant to the protocol: the cleaning index and the wash index. The cleaning index is defined as the ratio of the net flow Reynolds numbers over the oscillatory Reynolds numbers used in both the cleaning (Re_c) and the operation (Re_{op}) periods and represents the cleaning intensity:

$$\Psi = \frac{Re_c/Re_o}{Re_{op}/Re_o} = \frac{Re_c}{Re_{op}} \quad (1)$$

As the same oscillation conditions (Re_o) were used for the two production campaigns, the cleaning index is thus reduced to the format above.

The wash index is defined as the ratio of the washing volume (V_w) over the reactor volume (V_r), measuring the amount of waste generated in the cleaning phase:

$$\Omega = \frac{V_w}{V_r} \quad (2)$$

The cleaning of the COBR was performed by continuously pumping in first with tap water (pH = 7.3) at 60 °C, immediately followed by an industrial "free rinsing" cleaning solution (Liquinox - Solujet, 1% solution), and then the USP water at room temperature. The oscillation frequency and amplitude were 2 Hz and 40 mm, respectively. The cleaning index was 228. Samples taken from the washing (four per minute) were analysed and are shown in Figure 4. The vertical axis of Figure 4 is the remaining concentration of vanisal sodium during the washing process, while the horizontal axis is the volume of washing liquids employed, which is also related to the time of washing as later used in Figure 5. The dotted line in Figure 4 indicates the calculated maximum residual level of vanisal sodium (0.026 mg mL^{-1}) allowable when the COBR is changed over to produce aspirin, in accordance to the limits set by the International Pharmacopeia.[34] Note that the calculated level has also included a 100-fold safety factor. It can be seen that the COBR was clean even before the cleaning procedure had been completed. The wash index was 5.18, giving a total waste of 10.8 L.

The loss of product is defined as the ratio between the amounts of vanisal sodium lost in the cleaning over the total vanisal sodium produced. In the COBR this figure is 0.001%, which is significantly lower than the industry norm of 0.1−0.2%.[35] On this basis we were satisfied with the cleaning

(33) Lelieveld, H. L. M., Mostert, M. A., Holah, J., Eds. *Handbook of Hygiene Control in the Food Industry*; Woodhead Publishing: Cambridge, UK, 2005.
(34) Monographs: *Pharmaceutical substances: Acidum acetylsalicylicum - Acetylsalicylic acid*; World Health Organization (WHO)Geneva, 2008.
(35) Norton, E. *Visit to Piramal - Grangemouth*; Caldeira, R., Ed.; Nicholas Piramal India Ltd.: Grangemouth, U.K., 2009.

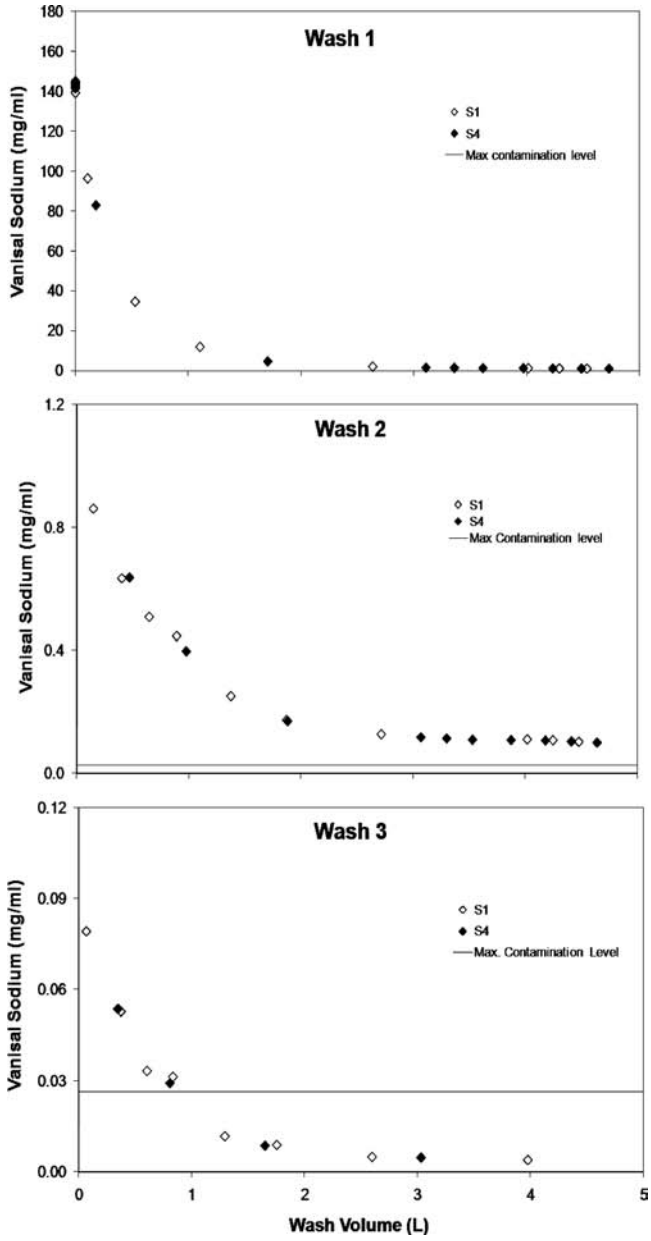


Figure 4. **Washing data for vanisal sodium. (Wash 1 - tap water, Wash 2 - detergent, Wash 3 - USP water).**

procedure and process we had chosen for the production of vanisal sodium.

From the washing data shown in Figure 4, the kinetics of the cleaning process can be evaluated by plotting $-\ln(C/C_0)$ against time in Figure 5, where C is the concentration of the studied chemical species at a given time t (mg mL^{-1}) and C_0 is the concentration of that chemical species at the start of washing (mg mL^{-1}). The linearity of the fits confirms a first-order kinetics for the washing process in the COBR, and the averaged rate constant is 0.0046 s^{-1}. Our data are in line with several other studies involving tubular equipment where cleaning was described as a first-order kinetics.[36–41]

Acetylsalicylic Acid. The synthesis and crystallization of aspirin was performed straight after the production of vanisal

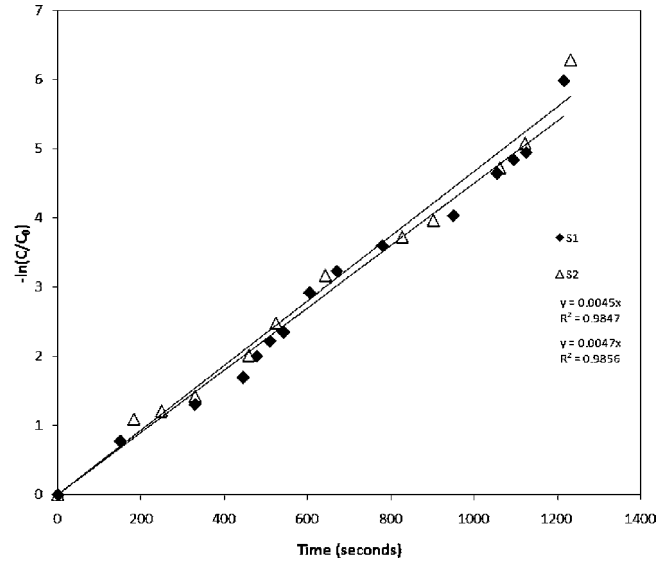


Figure 5. **Kinetics extracted from vanisal sodium cleaning data.**

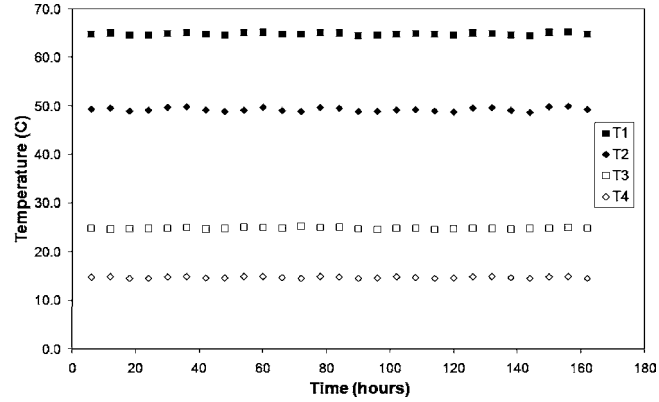


Figure 6. **Temperature measurements during the aspirin reaction.**

sodium and after the described washing protocol. Figure 6 shows the temperature profile of the aspirin reaction. It is evident that during the week-long synthesis the temperature profiles at each stage of the process remained consistent.

Figure 7 shows the amount of acetylsalicylic acid produced as a function of time. Once again we see that the production of aspirin is consistent over the course of the process, with very little scattering. The purity of the product analyzed by HPLC was 99.57% over 54 samples.

(36) Cabero, M. L.; Riera, F. A.; Álvarez, R. Rinsing of ultrafiltration ceramic membranes fouled with whey proteins: effects on cleaning procedures. *J. Membr. Sci.* **1999**, *154*, 239–250.

(37) Ni, X.; Liao, A.; Valentine, A. On the Crystal Polymorphic Forms of L-Glutamic Acid Following Temperature Programmed Crystallization in a Batch Oscillatory Baffled Crystallizer. *Cryst. Growth Des.* **2004**, *4* (6), 1129–1135.

(38) Lelievre, C.; Antonini, G.; Faille, C.; Bezenech, T. Modelling of Cleaning Kinetics of Pipes Soiled by Bacillus Spores Assuming a Process Combining Removal and Deposition. *Trans. Inst. Chem. Eng.* **2002**, *80* (C), 305–311.

(39) Jennings, D. W.; Weispfennig, K. Experimental Solubility Data of Various n-Alkane Waxes: Effects of Alkane Chain Length, Alkane Odd Versus Even Carbon Number Structures, and Solvent Chemistry on Solubility. *Fluid Phase Equilib.* **2005**, *227*, 27–35.

(40) Karlsson, C.; Whalgreen, M.; Tragardh, C. The Removal of β-Lactoglobulin from Stainless Steel Surfaces at High and Low Temperature as Influenced by the Type and Concentration of Cleaning Agent. *J. Food Process Eng.* **1998**, *21* (6), 485–501.

(41) Bourne, M. C.; Jennings, W. G. Kinetic Studies of Detergency. *J. Am. Oil Chem. Soc.* **1963**, *40*, 517–523.

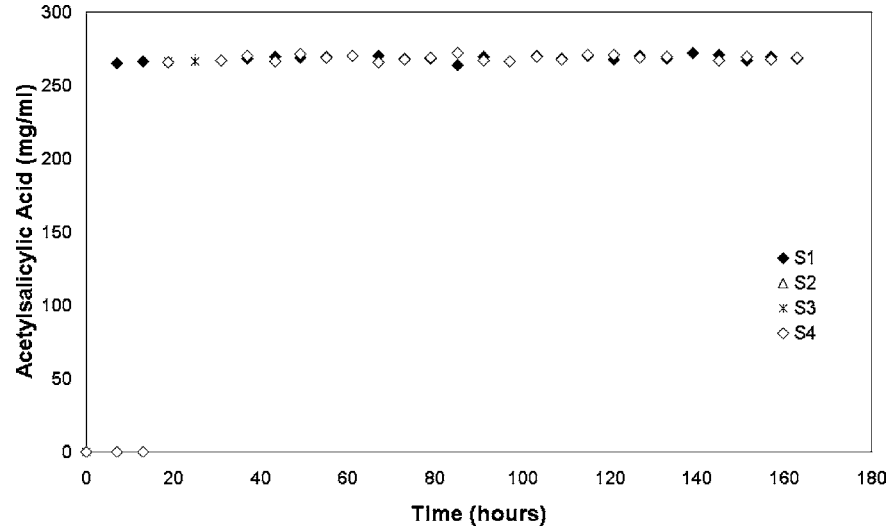


Figure 7. **Acetylsalicylic acid produced continuously in the COBR.**

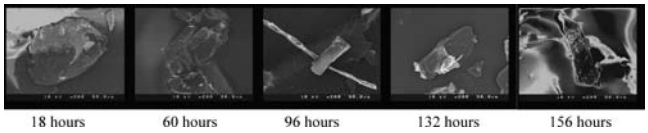


Figure 8. **SEM images of acetylsalicylic acid crystals sampled at location S4 in COBR.**

There has been recent controversy regarding the polymorphism of aspirin. Some authors claim that there is a second form of the acetylsalicylic acid crystal (classified as form II) in addition to form I, while others questioned its existence.[42−44] The SEM images taken from the samples at the location S4 in the COBR are given in Figure 8 for different times of operation. The crystals are of the plate-type form for all samples, which is consistent for the week-long operation. Our XRD results in Figure 9 confirm that the synthesized acetylsalicylic acid is of the form I, which is also consistent with that from literature.[45]

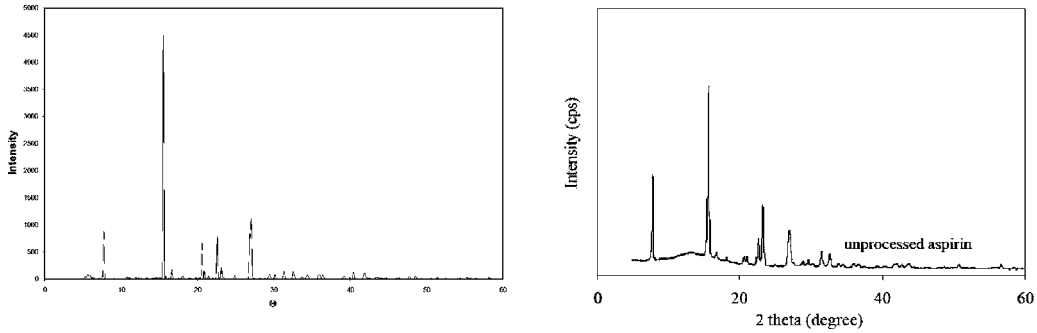
The cleaning procedure for the acetylsalicylic acid run is the same as that for vanisal sodium, i.e. pumping tap water, Liquinox - Solujet, 1% solution, and USP water in sequence, one immediately after the next. The same values of oscillation frequency and amplitude were also used during the cleaning. However, it is widely acknowledged that for pharmaceutical and biochemical products higher production and cleaning standards are required in comparison to those for chemical counterparts. Yet, there is no published guideline or information on how much higher it should be. As a rule of thumb, we applied a factor of 1.5 over and above that for vanisal sodium, giving the cleaning index of 336 for aspirin. Samples from the washing cycles were collected (four per minute) and analyzed and are shown in Figure 10. The dotted line indicates the calculated maximal contamination level for cleaning validation purposes in the manufacture of paracetamol,[34,46] which is another API to be produced after this cleaning process. The results of paracetamol will be reported in a different paper. The maximum amount of residual acetylsalicylic acid (BL_2) allowed in the COBR was calculated using the following expression:[46]

$$BL_2 = \left(\frac{\text{minimum daily dose of API}_A}{\text{minimum daily dose of API}_B}\right) \times 1000000 \times \text{SF}(\text{mg mL}^{-1}) \quad (3)$$

where API_A is acetylsalicylic acid (the active chemical in aspirin), API_B is paracetamol, and SF is the safety factor (1000). Note that the value of 1000,000 is from converting BL_2 to ppm (or mg mL^{-1}). BL_2 in this case was 0.113 mg mL^{-1}. Once again the COBR was cleaned after the washing had been completed. The loss of product due to the cleaning of the COBR amounted to 0.005% of the total amount of aspirin produced. This is also lower than the industry norm of 0.1−0.2%.[35] The swab sample test was performed at the location of V3 (Figure 1b) according to the method developed by Nozal et al.[47] and is also presented in Figure 10 (▲). The level from the swab sample is well below the dotted line. The result confirms that the cleaning of the reactor was effective. The wash index is 5.07 when the reactor is cleaned, which translates to 10.6 L of liquid waste.

The kinetics of the cleaning for aspirin was also evaluated, and a plot of $-\ln(C/C_0)$ against time is shown in Figure 11. As

(42) Bondioli, P. The preparation of fatty acid esters by means of catalytic reactions. *Top. Catal.* **2004**, *27* (1−4), 77–82.
(43) Vishweshwar, P.; McMahon, J. A.; Oliveira, M.; Peterson, M. L.; Zaworotko, M. J. The Predictably Elusive Form II of Aspirin. *J. Am. Chem. Soc.* **2005**, *127* (48), 16802–16803.
(44) Amato, I. Aspirin's Dose Of Structural Insight. *Chem. Eng. News* **2007**, *85* (1), 27–28.
(45) Cambeiro, L.; Jobson, J.; Pallay, M.; Smith, A.; White, C.; Yermakova, Y. Crystallization of Aspirin Crystals in Polar and Non Polar Solvents in the Presence of Surfactants: An Experimental Approach to Control Size and Shape of Crystals. *2006 Governor's School of Engineering and Technology Research Journals*; Rutgers University: New Brunswick, NJ, 2006.
(46) LeBlanc, D. Establishing scientifically justified acceptance criteria for the cleaning validation of API's. *Pharm. Technol.* **2000**, *24* (10), 160–168.
(47) Nozal, M. J.; Bernal, J. L.; Toribio, L.; Jiménez, J. J.; Martín, M. T. Validation of the removal of acetylsalicylic acid: Recovery and determination of residues on various surfaces by high performance liquid chromatographic. *J. Chromatogr., Sect. A* **2000**, *870* (1−2), 69–75.



a) from COBR b) from literature[45]

Figure 9. **XRD results for the acetylsalicylic acid crystals.**

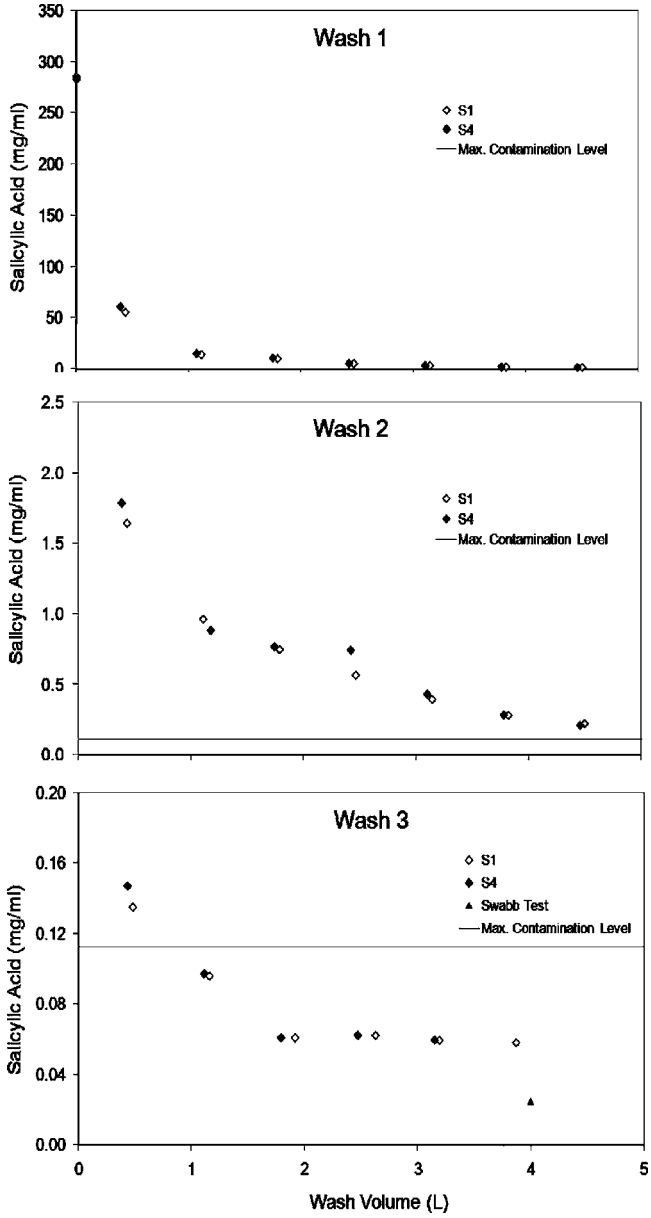


Figure 10. **Washing data for aspirin. (Wash 1 - tap water, Wash 2 - detergent, Wash 3 - USP water).**

was in the vanisal sodium case, the first-order kinetics is well suited to describe the cleaning process. The mean rate constant is 0.006 s^{-1}.

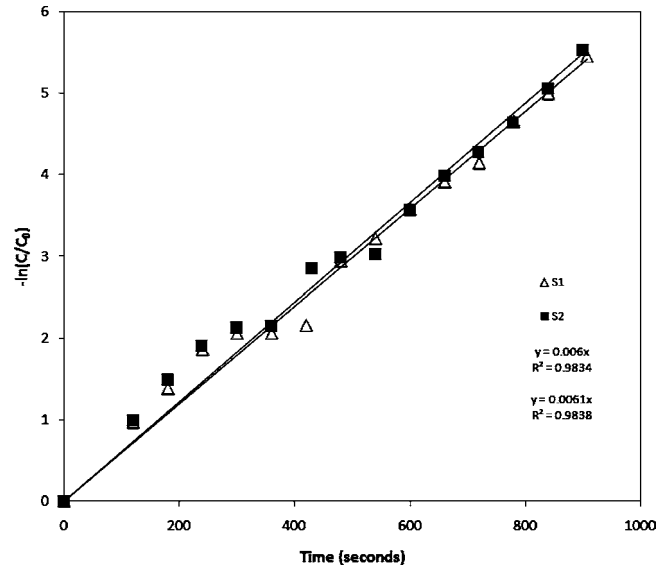


Figure 11. **Kinetics extracted from aspirin cleaning data.**

The time used for each of the washing processes is considerably smaller than the corresponding total operation time, e.g. the ratios between the operation and the cleaning times for vanisal sodium and acetylsalicylic acid were 362.6 and 530.5, respectively. For the two washing processes a higher cleaning index was applied for aspirin in comparison to that for vanisal sodium, a higher rate constant for aspirin cleaning was expected, i.e. $k_{aspirin}/k_{vanisal\ sodium} = 1.3$. This indicates that at the identical oscillation conditions, the rate constants for the cleaning of the COBR depend on the cleaning intensity that is controlled by the net flow, as suggested previously by Bird et al.[48] This is understandable as the washing process can largely be regarded as a physical process in which mixing plays an important part. It should be noted, however, that while there are many factors influencing the cleaning efficiency, e.g. the nature of the fouling substance, the flow rate, the cleaning temperature, the shape and nature of the cleaned surfaces or the nature and concentration of the cleaning solution, it is not feasible to establish an explicit correlation between previous studies and this work. Table 1 compiles the kinetics data for other cleaning studies in

(48) Bird, M. R.; Fryer, P. J. An experimental study of the cleaning of surfaces fouled by whey proteins. *Food Bioprod. Process.* **1991**, *69c*, 13–21.

Table 1. **Comparison of cleaning data from different studies (s.s. - stainless steel)**

authors	cleaning solution	fouling substance	net flow velocity (m/s)	temperature (°C)	cleaned surface	k (s^{-1})
our data	tap water Liquinox 1% USP water	vanisal sodium	0.043	60 RT[a]	COBR (glass/PFA)	0.0045
our data	tap water Liquinox 1% USP water	aspirin	0.064	60 RT	COBR (glass/PFA)	0.0061
Jennings (1963)	NaOH 0.03 M	tristearin	0.095	−	s.s. strip in a glass pipe	0.023
Karlsson (1998)	NaOH 0.1−0.2 mg/mL	β-lactoglobulin	0.033	24	s.s. cell	0.048−0.086
Lelievre (2002)	NaOH 0.5%	*Bacillus* spores	0.2−3.3	60	s.s. pipe	0.0012−0.083

[a] RT = room temperature.

tubular type of reactors for indication only. On this basis, the rate constants from this work are comparable to these from the prior arts.

Conclusions

This contribution reports our experimental studies of two organic syntheses performed in a tandem fashion in a COBR. Consistent yields were obtained for the duration of the experiments, and the data gathered in this study suggest that the COBR design is well suited to the syntheses of high-purity APIs and fine chemical products. The cleaning protocol is effective and efficient with a minimal amount of waste generated, in accordance to Good Manufacturing Practice (GMP) and Good Laboratory Practice (GLP) standards. The cleaning kinetics is of a first order, which is compatible to those of previous work.

Acknowledgment

We thank the EPSRC and NiTech Solutions Ltd. for sponsoring this work, Mr. Matthew Tidmarsh of the CIKTN for coordinating the project, and NiTech for allowing the use of analytical equipment. R.C. also thanks Dr. Lihua Zhao of NiTech for the discussions and assistances received.

Received for review May 8, 2009.

OP900120H