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Development of a Continuous Schotten−Baumann Route to an Acyl Sulfonamide

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Supporting Information

ABSTRACT: The development and scale-up of a synthetic route to tasisulam sodium (5-bromo-thiophene-2-sulfonic acid 2,4-dichlorobenzoylamide sodium salt, hereafter referred to as tasisulam) utilizing continuous Schotten−Baumann reaction conditions is disclosed. A new synthetic route for the cytotoxic API amenable to continuous processing was envisioned that would minimize potential worker exposure by reducing the number of unit operations and would allow commercial-scale API production in laboratory fume hoods with inexpensive glassware. The developed Schotten−Baumann conditions contained fewer unit operations than the existing batch process by utilizing the direct formation of the final sodium salt from a sulfonamide and acid chloride without isolation of the free acyl sulfonamide. Batch development, continuous proof of concept studies, 5.2 g/h lab-scale demonstration and 5 kg/day commercial-scale runs will be discussed. Very stringent release specifications were in place for the tasisulam API batch process, and the challenges of meeting these requirements for the continuous process are detailed. Finally, the quality of material generated during startup and shutdown transitions will be addressed.

INTRODUCTION

Continuous processing has received renewed attention recently in the pharmaceutical industry due to the advantages this processing methodology can impart. Several of the typical reasons for continuous processing include safety advantages resulting from minimizing volumes and maximizing heat transfer rates for reactions with hazardous reagents, potential for thermal runaway or large exotherms.[1] In the pharmaceutical industry, continuous processing has greatly improved safety for reactions with hydrazine, bromonitromethane, diazomethane, sodium cyanide, methanesulfonyl cyanide, and cyanogen chloride, some of which were used in processes to generate >100,000 kg/year advanced intermediates.[2] Continuous processing can also easily achieve extreme temperatures less than −40 °C and greater than 200 °C. Another reason to develop a continuous route is to provide improvement for a specific step by optimizing a reaction parameter (purity, time, etc.)[3] or by taking advantage of a novel or narrow processing window.[4] Furthermore, the FDA has highlighted the importance of enabling continuous processing to ensure product quality with the benefits of operating at steady state and the opportunity to continuously monitor process streams using process analytical technology (PAT) which fits well with quality by design (QbD).[5] These are all excellent and well-known reasons to use continuous processing. In this contribution we aim to communicate that another impactful use of continuous processing is cytotoxic API production in inexpensive, dedicated, "disposable" equipment sets for production of low volume (<1000 kg/year) cytotoxic compounds in laboratory fume hoods.

Herein we describe methodology that focuses on a fully continuous process covering multiple unit operations and steps of a synthetic route. An important aspect of this approach relies on continuous crystallization which has been practiced in industry for several decades.[6] Two categories of continuous crystallizers used in R&D in the pharmaceutical industry are tubular plug flow reactors (PFR)[7] and mixed suspension mixed product removal (MSMPR) stirred tank crystallizers.[8] Research-scale MSMPRs are well described in the literature on crystallization of inorganic compounds.[9] One of the main benefits of PFR crystallizers is the ability to achieve small controlled particle size with narrow crystal size distribution (CSD). Relatively high supersaturation is controlled along the length of the PFR crystallizer. CSD was not a goal of the current work, because the tasisulam API is redissolved during formulation; therefore, the primary goal of this API crystallization was impurity rejection and the quality control benefits of steady-state operation. MSMPRs in series were chosen for design and development of a continuous process because of the quality control benefits of steady-state low supersaturation at all times. The design, development, and scale-up of a continuous Schotten−Baumann process for tasisulam sodium will be highlighted here.

Tasisulam (**LY573636·Na**) is a novel anticancer agent that is classified as a cytotoxic compound and has been shown to initiate apoptosis.[10] The ability to synthesize tasisulam in a continuous fashion, taking advantage of equipment small enough to fit in laboratory fume hoods, would minimize the potential for operator exposure. In addition to running in laboratory fume hoods, this equipment enables "tech transfer by truck" where dedicated equipment could be utilized in a different location by transporting the equipment to another facility. A continuous process also opens up the possibility of

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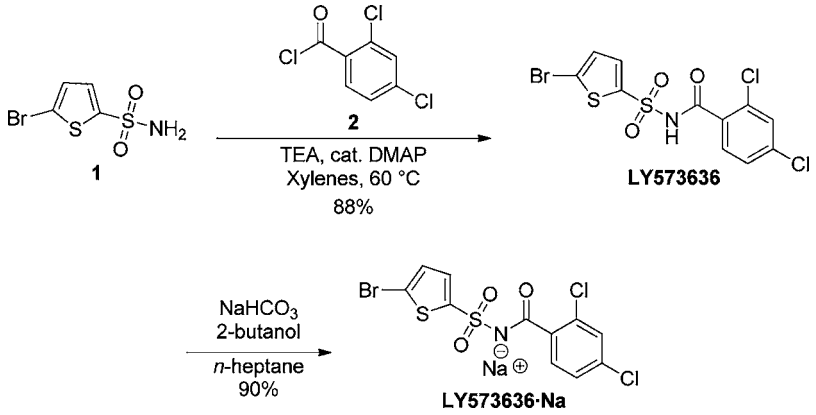
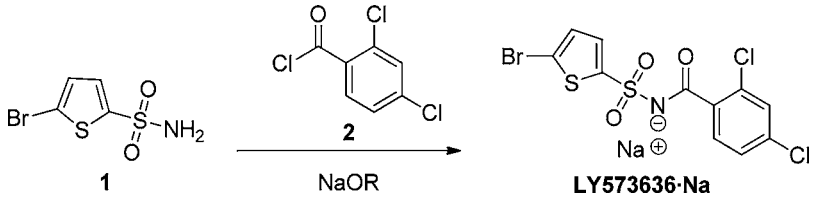
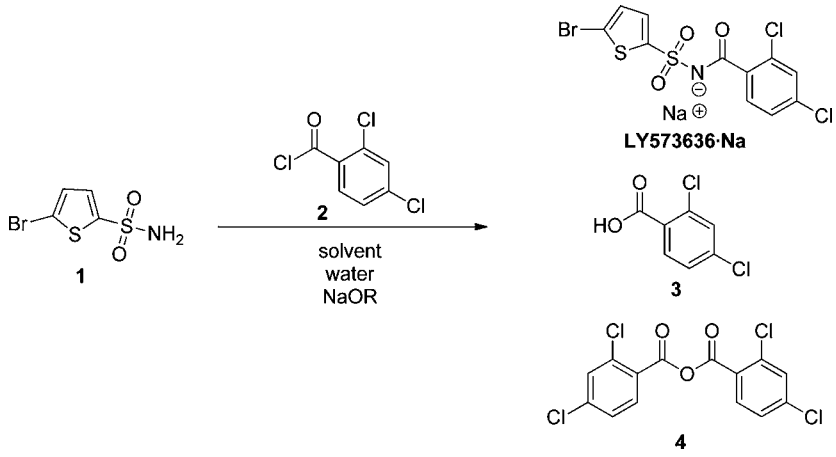
Scheme 1. Batch process for the synthesis of tasisulam



Scheme 2. Proposed direct formation of sodium salt



Scheme 3. Schotten–Baumann route to tasisulam and key impurities



utilizing dedicated, portable, and disposable equipment for a single API, eliminating the potential of cross-contamination. Cross-contamination is avoided in traditional batch processing in multi-use equipment by utilizing the appropriate cleaning protocol. However, for short campaigns of low-volume, cytotoxic API, it is conceivable to spend more time and solvent cleaning after the campaign than actually making the API. The costs associated with dedicating a contained plant module with fixed batch equipment would represent a significant capital investment compared to dedicating a kilo lab space with standard fume hoods.

As for any case where a new route is being considered to replace existing chemistry, a new process would have to deliver a similar yield along with meeting the same key quality attributes. To help ensure the impurity profile for the final API was met in the narrow time frame that was available, the first attempt at a continuous route employed slight modifications to the existing two-step batch synthetic route. In the end, however, the best continuous process did in fact have different reagents and fewer isolations compared to the best batch process, although both processes were very good.[11] This is not surprising, given that continuous processing enables operating modes not practical in batch mode, such as countercurrent multistage extraction, and the small scale of operation allowed the use of automated repeating semibatch strip-to-dryness solvent exchange. Conversely, a batch process can enable operating modes which are challenging for small-scale continuous processing such as charging solids.

Solubilized Batch Process Development. Development work started with identifying conditions that would make the existing batch process amenable to continuous processing. The batch process for tasisulam (Scheme 1) involved the two-step process of isolating the free acyl sulfonamide and then subsequent formation of the sodium salt, producing API in high purity and yield over two steps.[12] To establish robust process stream transfers, the existing process was converted to a "solubilized batch" process where all streams between unit operations were homogeneous at room temperature with the

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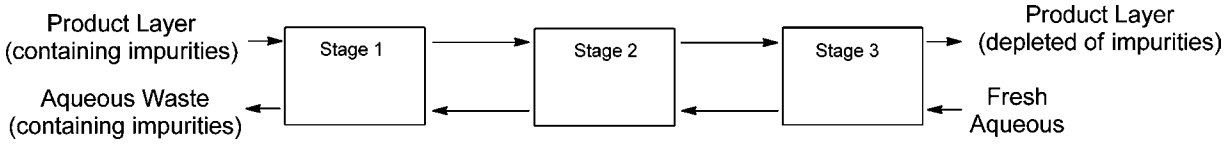

Figure 1. Countercurrent extraction.

exception of the two continuous crystallizations where the transfer of a slurry to a filter was employed. This was accomplished by changing process solvents and switching from triethylamine to Hunig's base along with antisolvent crystallizations which resulted in reproducible solid isolations for both the free acyl sulfonamide and sodium salt by continuous crystallization.

Compared to the existing batch process, this solubilized batch process running in continuous equipment did not provide an advantage in terms of the number of unit operations, number of isolations, plant footprint, cycle time, operating cost, or yield, and PMI was almost double. Therefore, it was not worth pursuing the switch from batch to continuous for these conditions. Rather than fit the continuous process within the constraints of the batch process, the best continuous route was most likely one which was designed with the advantages that continuous processing could provide.

Batch Development of a Continuous Process. As mentioned previously, the cytotoxic nature of both the free acyl sulfonamide and sodium salt raised industrial hygiene concerns of worker exposure. Thus, the number of unit operations could be substantially reduced if the acyl sulfonamide and sodium salt formation could be accomplished utilizing a single reaction, eliminating a solids isolation. Utilization of sodium alkoxides was investigated as the starting point for this transformation as shown in Scheme 2. These conditions were very promising and were optimized utilizing sodium amylate but were complicated by the precipitation of the sodium salt of the sulfonamide **1** and unacceptable levels of **1** remained at the end of reaction. The precipitation of solids in the reaction on its own was not the problem, but rather the decreased conversion did not warrant further development of the alkoxide chemistry.

The sodium salt of **1** has good solubility in water, and with this in mind the possibility of pursuing Schotten–Baumann conditions was considered (Scheme 3). These conditions had been previously investigated during the initial development of the existing batch process and utilized aqueous sodium hydroxide with toluene. When these conditions were optimized to drive the reaction to completion, elevated levels of the benzoic acid **3** were present at reaction conclusion, and **3** had poor solubility in crystallization solvents, thus preventing rejection in solid isolations. However, when this problem was considered with continuous processing in mind, it was perceived that a countercurrent extraction operation as shown in Figure 1 would prove beneficial.[13] For this to be successful, the sodium salt of **3** would need to preferentially partition into the aqueous phase while being excluded from the organic phase, also resulting in the partitioning of **LY573636·Na** back into the organic layer in stage 1. The product is water-soluble, but partitioning of product into the organic phase in stage 1 is favorable because of the high concentration of dissolved species in the aqueous phase. Pure water can be used in countercurrent multistage extraction because the aqueous phase only exits from stage 1 which is highest in concentration of other solutes.

As mentioned previously, the toluene and sodium hydroxide conditions that were examined resulted in high levels of benzoic acid **3**; thus, 2-MeTHF with tetrabutylammonium bromide (TBAB) was chosen as the starting point for the batch optimization of the Schotten–Baumann conditions.[14] Very promising reaction conditions were observed that utilized 1.2 equiv of acid chloride **2** as seen in Table 1. The switch from sodium hydroxide to sodium carbonate provided improvement, but room temperature reaction conditions led to a buildup of anhydride **4** resulting from reaction of the acid chloride **2** with benzoic acid formed by hydrolysis. The anhydride **4** was a reactive intermediate that was also converted to product by reaction with **1** but at a slower rate. Also, when only 5 volumes of 2-MeTHF were utilized, the product and byproduct sodium bicarbonate precipitated from solution. The switch to isopropyl acetate avoided the issue of **LY573636·Na** insolubility, and increasing the volume of water ensured the bicarbonate remained in solution. Overnight stirring allowed the extra reaction time necessary to consume the intermediate anhydride resulting in less than 1% starting sulfonamide at the end of the reaction (entry 4). Further improvement was observed when the reaction temperature was increased to 65 °C resulting in less than 1% starting sulfonamide **1** once addition of the acid chloride was complete (entry 5).

Table 1. Batch screening of Schotten–Baumann reaction conditions to synthesize tasisulam

entry	base (2.2 equiv)	solvent system	temp. (°C)	acid chloride **2** equiv[a]	sulfonamide **1** HPLC area %
1	NaOH	5 vol 2-MeTHF 5 vol water	22	1.2	18.7
2	Na_2CO_3	5 vol 2-MeTHF 5 vol water	22	1.2	8.5
3	Na_2CO_3	5 vol isopropyl acetate 5 vol water	22	1.2	5.2
4	Na_2CO_3	7.5 vol isopropyl acetate 10 vol water	22	1.2	0.6
5	Na_2CO_3	7.5 vol isopropyl acetate 10 vol water	65	1.2	0.8

[a]For all reactions, the acid chloride was added over 30 min, and reaction completion samples were pulled as soon as addition was complete with the exception of entry 4 which was allowed to stir for 26 h.

With the encouraging reaction conditions that had been developed it was important to consider three additional impurities that have not already been discussed as shown in Figure 2, and the amidine compound **7** was of particular interest. It was known from previous work that the rejection of

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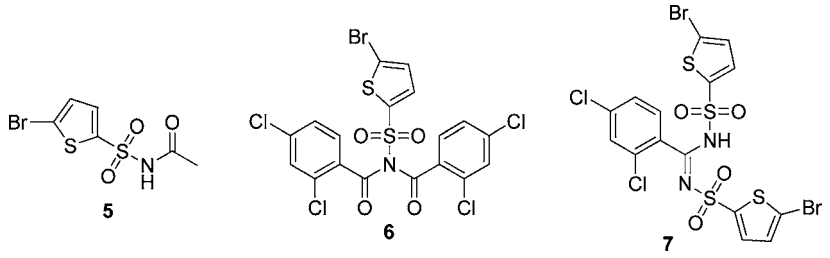

Figure 2. Impurities generated during the acyl sulfonamide formation.

high levels of this impurity would be problematic, but gratifyingly the best conditions examined (entry 5) produced only 0.33 HPLC area % of this impurity.

The next step in development was to consider changes that would translate to a more efficient continuous process. As discussed previously, reagent addition and hence process stoichiometry is more robust with soluble feed streams so the first priority was to identify homogeneous solutions for all reagents at room temperature. The second priority was to prevent solid precipitation between unit operations. The switch to 7.5 vol isopropyl acetate solved solubility issues for the end of reaction conditions[15] but starting sulfonamide **1** had poor solubility in this solvent. From the previous work, sulfonamide **1** had shown good solubility in 2-MeTHF and as expected, addition of 1.5 vol of 2-MeTHF to the 7.5 vol of isopropyl acetate provided the required solubility. The acid chloride **2** was added as a neat liquid in the experiments in Table 1, and although the acid chloride was a liquid at room temperature, its freezing point (16−18 °C) introduced the possibility of plugging in transfer lines.[16] One volume of toluene was employed to ensure the acid chloride feed would remain homogeneous. Finally, as mentioned previously, 10 volumes of water was utilized to make up the sodium carbonate stream to ensure the byproduct sodium bicarbonate remained in solution.

The two fundamental types of continuous reactors are plug flow (PFR) and stirred tank (CSTR). Either would work for this Schotten−Baumann reaction, and kinetics of the main reaction measured during batch experiments could be used to design either reactor type to achieve required conversion of reagents. The main questions that needed to be answered were whether the optimum reagent stoichiometry and the resulting profiles of minor impurities would be different for the different reactor configurations. Research-scale batch reactions were run using three different modes of reagent addition to predict differences in impurity profile for a standard batch reaction compared to those run in CSTRs or PFR. In all three cases, reaction temperature and time were approximately the same, but method of reagent addition was changed. The standard batch-controlled addition process started with **1** in the flask at temperature, and 1.2 equiv of **2** were added over 1 h so molarity of **1** was high relative to that of **2** until the end of the reaction. Co-addition of both **1** and **2** at a constant stoichiometric ratio (1:1.2) was done to mimic the impurity profile that would result from CSTRs, resulting in a slight excess of **2** to **1**, but both are small relative to product concentration at all times. Finally, all-at-once addition of **2** to a solution of **1** already at temperature to mimic impurity profile that would result from a PFR where there was a slight excess of **2** relative to **1**, but concentrations of both were high compared to product for most of the reaction time. Greater than 99% conversion of **1** was achievable for all three reaction methods, but impurity profiles were measurably different. Amidine **7** decreased from 0.36 HPLC area % for standard batch to 0.31 for a coaddition and 0.26 for all-at-once addition. While the lower level for this impurity is appealing for the all-at-once addition, 1.32 equiv of **2** were required for all at once addition, compared to 1.2 equiv of **2** for slow addition, to achieve the same conversion of **1**. An additional consideration for choice of reactor type in this case is the evolution of carbon dioxide during the reaction which would result in a third phase in a PFR but would easily partition into the headspace of a CSTR. CSTRs also provide the benefit of dampening out temporary inaccuracies in flows without wide swings in the effective stoichiometry when compared to PFR. Also, the impurity profile was sensitive to the rate of mixing resulting in higher levels of the anhydride **4** when mixing was poor. Longer reaction times could be utilized to decompose this impurity, but overall this led to a preference for CSTRs because scale-up of liquid−liquid mixing is less dependent on flow rate and therefore residence time for a given reactor. In contrast, mixing rate in a PFR depends on flow rate, and there is no mechanical mixing in the event that flows must be temporarily halted in production. Once CSTRs were chosen as the desired mode of addition, several other key observations were made during the course of simulated CSTR runs. TBAB was not necessary because equivalent results were observed with and without the phase transfer catalyst. Equivalents of acid chloride (1.3 and 1.4) were screened for changes in impurity profile and with the exception of increased benzoic acid and anhydride levels, no issues were observed. When only 1.05 equiv of **2** was used, undesirable levels of starting sulfonamide **1** were observed, and the level of the amidine impurity **7** increased to 0.5 % HPLC area %. No unusual increase in color or unexpected changes in the physical characteristics of the reaction were observed for any of these runs. Most importantly, an acceptable impurity profile was observed for all scenarios utilizing these Schotten−Baumann conditions, comparing coaddition of **1** and **2**, versus slow addition of **2** to **1**, versus all-at-once addition of **2** and **1**. This showed that acceptable impurity profile would be achieved in CSTRs, although it would not be exactly the same as batch or PFR.

The crystallization was also developed in batch mode before attempting to run continuous in MSMPRs. Several room-temperature antisolvent crystallization conditions were examined. Isopropyl acetate, isobutyl acetate and *n*-butyl acetate were all very good at solubilizing **LY573636·Na**, and addition of heptane as antisolvent resulted in well-behaved crystallizations but resulted in material with lower purity than desired. Alcohols resulted in better impurity rejection, but the lower solubility in these solvents would require high volumes to generate a soluble feed stream. After screening a variety of conditions, a combination of isopropyl acetate and isopropanol was the best resolution to this issue combining the best aspects of both solubility and impurity rejection. After optimization, the

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final conditions for the crystallization utilized a 3:2 v:v isopropyl acetate/isopropanol feed at 3 vol with a 10 vol heptane antisolvent addition at room temperature. The solubility of the key impurities was examined in this solvent system with higher and lower levels of heptane as seen in Table 2. This data ensured that the anticipated levels of sulfonamide

Table 2. Solubility of key impurities at room temperature[a]

compound	1.2:1.8:5 v:v IPA/iPrOAc/Hep (wt %)	1.2:1.8:10 v:v IPA/iPrOAc/ Hep (wt %)	1.2:1.8:12 v:v IPA/iPrOAc/ Hep (wt %)
sulfonamide **1**	2.14	0.52	0.29
benzoic acid **3**	10.53	6.74	5.99
amidine **7**	0.35	0.11	0.08

[a]For comparison, a typical 27 wt % **LY573636·Na** feed stream in 3 vol of 2:3 v:v IPA/iPrOAc for the crystallization contains 0.11 wt % sulfonamide **1**, 0.09 wt % benzoic acid **3** and 0.08 wt % amidine **7**.

1, free benzoic acid **3**, and amidine **7** would be readily purged by the planned solvent system for the crystallization, while the sodium salt of **3** would be removed by the extraction. One of the main benefits of running antisolvent crystallizations continuous rather than batch is the potential for a larger ratio of dissolving solvent to antisolvent. This allows the crystallization to start out with higher concentration solutions initially with the potential for higher yields and throughput.

Once the crystallization system for the product was finalized, the planned displacement of the toluene/isopropyl acetate/2-MeTHF product solution to 3:2 v:v isopropyl acetate/ isopropanol could be examined. This was readily accomplished on a rotary evaporator concentrating the extraction product to a foam, add-back, and dissolution in 3 vol of 3:2 isopropyl acetate/isopropanol followed by a second concentration to a foam with a second add-back with 3:2 isopropyl acetate/ isopropanol to generate the crystallization feed. The second strip plus add-back was necessary to ensure toluene, a potential antisolvent for the product, and water, a very effective solubilizing agent for product, were at low levels. Normally, distillation with strip to dryness is not considered a viable option for manufacturing, but for a low-volume product such as **LY573636·Na** strip to dryness is an option. If fact, our automation system can run multiple rotary evaporators in parallel with a single flow cart at high frequency of volume turnover, and moreover >400 L/day throughput is possible for solvent exchange with strip to dryness in this equipment.

Continuous Proof of Concept. The goal for the process was to design and develop a continuous reaction, extraction, and crystallization with automated repeating semibatch solvent exchange and semibatch filtration and batch drying. The continuous unit operations were designed and developed for reaction in CSTRs in series, extraction in three-stage countercurrent mixer−settlers in series, and crystallization in a cascade of two MSMPRs in series. Schematic drawings of the pilot-scale versions of these continuous unit operations are shown in Figures 8, 9 and 11. At research scale the temperature in each CSTR was controlled via a JKEM controller connected to a heating mantle and redundant thermocouples were tied into the system to record temperature data in DeltaV. The two-phase mixture from the CSTR reactors was pumped into stage 1 of the continuous mixer−settlers, and water was pumped into stage 3. After batch solvent exchange the dissolved API was pumped into the MSMPRs for continuous isolation. Dual glass syringe pumps were used for pumping homogeneous solution feeds to reaction, extraction, and crystallization at the 5.2 g/h scale.[17] All feed bottles were pressurized to 10 psig to provide net positive suction head to the pumps and placed on balances that were tied into DeltaV[18] to monitor flow rate accuracy over time. Transfer zone pumping technology has been previously disclosed[19] as an effective system for intermittent pumping of solid/liquid slurry out of each crystallization MSMPR. In this method, four automated block valves and a pressure swing chamber pull a specific volume of fluid from one vessel under vacuum and then push it into the next vessel by pressure from an inert gas. Operating in this fashion allows the height of the dip tube to set the liquid volume in the stirred tank, for both reaction and crystallization vessels. The main benefit of intermittent flow for continuous crystallization was that it enabled sufficient slurry velocity to prevent settling of solids in the transfer zones from the first MSMPR to the second, and from the second MSMPR to a single-plate pressure filter, which minimized the potential for solids plugging and fouling and minimized mean residence time of slurry in tubes between vessels.

The main goals of the 5.2 g/h continuous research and development runs were to examine product yield and impurity profile in each unit operation.[20]

(1) Continuous reaction: Experimental parameters were the number of CSTRs in series (2 vs 3), temperature, τ, stoichiometry of acid chloride **2** relative to sulfonamide **1**, and intermittent flow frequency. The effects of these parameters were measured with respect to product yield, conversion of sulfonamide **1**, and minimizing impurities with emphasis on anhydride **4**, bisacylated compound **6**, and amidine **7**.

(2) Continuous countercurrent extraction: Experimental parameters were τ, mixing rate, and organic to aqueous flow ratio. The effects of these parameters were measured with respect to product yield and removal of key impurities, in particular the sodium salt of **3** and acylated sulfonamide **5**.

(3) Continuous crystallization: The experiments were designed to study the time required to reach steady state, product yield, supersaturation in both MSMPRs at steady state, and rejection of key impurities generated including residual sulfonamide **1**, benzoic acid **3**, and amidine **7**.

Over the course of 24 h on three separate days, reaction conditions at 50, 65, and 80 °C were examined to monitor impurity levels and reaction completion. The three reagent solutions pumped continuously into the first CSTR of a two-CSTR reaction system, and from the second reaction CSTR, the reaction mixture flowed to the extraction unit operation where three mixers and settlers running in a countercurrent fashion were utilized to purify the product. Three volumes of toluene with respect to **1** fed continuously to the first extraction mixer to improve the phase separation, and 2 vol of water with respect to **1** was continuously pumped into the third mixer to provide the clean water wash required to remove benzoic acid and inorganics. All continuous vessels were started up in batch mode and filled to the desired operating levels before flows began.

As expected on the basis of the semibatch experiments with slow coaddition, higher reaction temperatures showed an increase in amidine **7** compared to lower reaction temperatures, so a clear starting point for the reaction in subsequent runs was

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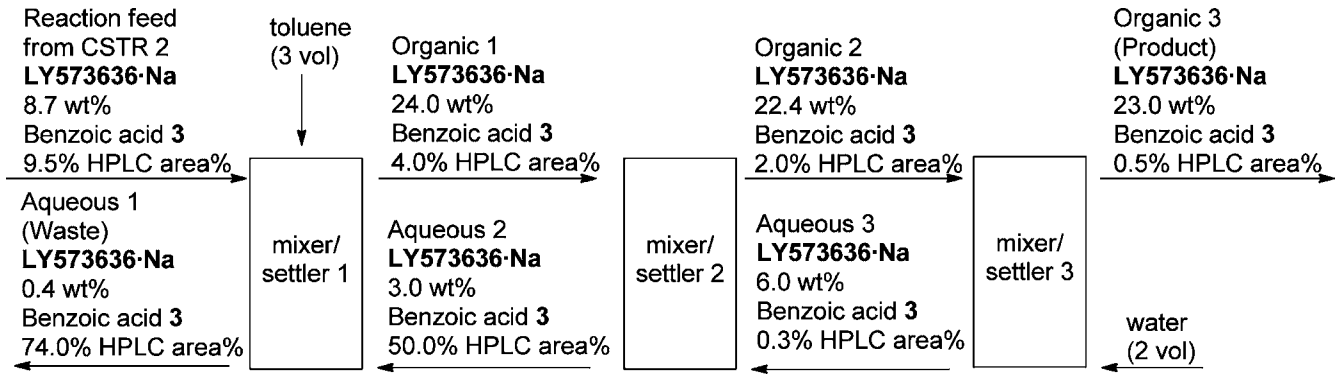

Figure 3. Countercurrent extraction of Schotten–Baumann proof of concept run.[21]

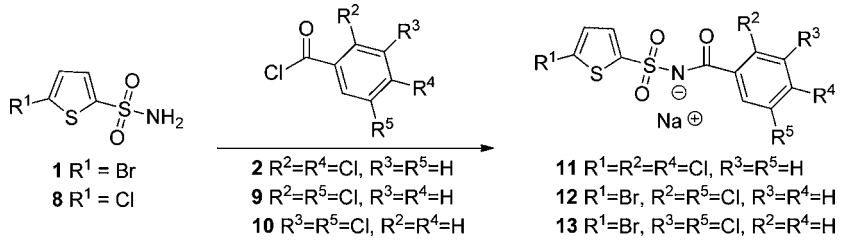

Figure 4. Impurities resulting from purity profile of incoming starting materials.

to start at 50 °C. The data for the extraction were also very promising as they showed the desired benzoic acid purge with minimal product loss. The countercurrent extractions in Figure 3, where all arrows represent continuous flow, show the starting HPLC area % for the benzoic acid **3** was 9.5%, but the final product solution continuously exiting settler 3 contains only 0.5% after fresh water wash. For **LY573636·Na**, the same fresh water wash pulled a significant amount of product (6.0 wt %) into the aqueous layer continuously exiting settler 3, and as the level of inorganics increased going into mixer 1, this material was partitioned back into the organic layer, and only 0.4 wt % product was lost to the aqueous waste continuously exiting settler 1. The key feature of this extraction is that the aqueous phase only exits the system from stage 1 which has the highest concentration of salts. The partition coefficient of **LY573636·Na** into the organic phase is 1.65 ± 0.15 in stage 3 but 49.4 ± 4.2 in stage 1, while the trend for benzoic acid **3** into the aqueous is 11.2 ± 4.6 for the third stage and 5.41 ± 0.14 in the first.

Prior to additional continuous runs, the possibility of diluting the acid chloride with a total of 4 vol of toluene was considered. This switch would eliminate a pump, feed tank, and mass flow control and monitoring from the system. A semibatch experiment with slow coaddition examining this change in the reaction feeds showed no changes in the reaction purity profile. With the proposed feed streams finalized, stability of these feeds and the reaction streams for all unit operations were examined. Over 30 days, the acid chloride feed stream and the sulfonamide solution showed no degradation in the proposed materials of construction for each of the two feed tanks on scale. The process streams for all unit operations were held at temperature over the course of seven days, and no degradation was observed. These findings were especially appealing because this allows the entire reaction train to be viewed as a hold point. Thus, the impact of an equipment malfunction or other interruption would be minimal because all flows could be stopped while issues were corrected with no need to divert material for purity reasons. From a more practical point of view, this would allow for easier examination of the reaction conditions on the 5.2 g/h scale runs during the development phase, permitting shutdown of the reaction, extraction and crystallization and holding overnight allowing the run to resume the next day near the steady-state conditions from the previous day.

Since tasisulam was in advanced clinical trials, the need for the continuous process to generate high-purity API that met the existing specifications cannot be understated. Thus, it is important to mention the impurity control strategy prior to the commencement of the continuous runs. As discussed previously, it was envisioned that the sodium salt of benzoic acid **3** would be removed via the countercurrent extraction. The sodium salt of the acylated sulfonamide **5** also has very high aqueous solubility and would be removed in a similar fashion. Two additional impurities, the anhydride **4** and the bisacylated compound **6**, were both reactive intermediates. The anhydride could react with an equivalent of the starting sulfonamide **1** to generate desired product and an equivalent of benzoic acid **3**. Compound **6** resulted from the reaction of tasisulam with an equivalent of the acid chloride, but this impurity hydrolyzes to generate an equivalent of desired product and benzoic acid **3**. The levels of amidine impurity **7** were monitored closely and results from the reaction of **6** with a second equivalent of sulfonamide via the mechanism that has previously been disclosed.[12] Unlike the other impurities this impurity has no decomposition or reaction pathways and no appreciable aqueous solubility so the final crystallization will have to purge this impurity to the required levels. This placed an extra burden on the continuous process with only one solid isolation compared to the two solid isolations in the previous batch process. However, as shown in Table 2, the crystallization had been designed to remove the amidine impurity as typical levels in the precrystallization feed were 0.08 wt % but the solubility in the crystallization matrix was 0.11 wt %. The mass flow ratio of crystallization matrix to crystallization feed solution was

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about 3:1, therefore the crystallization process could have rejected up to 0.3 wt % in the crystallization feed solution.

In addition to the impurities generated in the process, three additional isomeric impurities are important to discuss and compare to the original batch process. The 2,5-dichloro isomer **9** and 3,5-dichloro isomer **10** are both present in the starting acid chloride (Figure 4). The 3,5-isomer **10** has reliably been below 0.05 HPLC area % in all commercial samples of **2**, and the resulting acyl-sulfonamide from reaction with **1** to form compound **13** was not purged in the batch process. However, compound **11** resulting from the 2,5-isomer **9** present in the acid chloride was usually observed at approximately 0.10 HPLC area % in commercial samples of **2**. The existing batch process effectively reduced the levels of this impurity when the free acyl sulfonamide of tasisulam was isolated, but no further reduction was observed upon isolation of the sodium salt. This was a very important consideration since the goal of the continuous route was to avoid the free acyl sulfonamide isolation, and the ability to purge **11** at the sodium salt stage may be very similar. Finally, the chloro isomer **8** resulting in the formation of impurity **11** was not purged in the existing batch process, so this impurity had to be controlled by the purity of the incoming starting sulfonamide material **1**.[12]

Continuous Development. The next stage in development was to demonstrate the entire continuous process at 5.2 g/h scale with all four unit operations to further refine the flow conditions and evaluate important variables. The POC utilized two CSTRs in series as the starting point based on the reaction kinetics that were observed during batch experiments. During this phase of development, it was planned to run the process train for 12 h per day to ensure that steady state could be attained in the entire nine-vessel reaction−extraction train. The 5.2 g/h run was started with conditions that minimized the amidine formation based on data generated during the POC run. The starting reaction conditions would be 1.3 equiv of the acid chloride **2** at 50 °C and utilization of two CSTRs with a 30 min mean residence time for each CSTR with 7 min intermittent aging for complete conversion of starting material **1** in the second CSTR. During the first day of the 5.2 g/h run, these conditions appeared to be working rather well generating 0.29% of amidine **7** impurity while leaving only 0.33% unreacted starting sulfonamide **1**. However, higher levels of the anhydride **4** at 14.3 HPLC area % were unexpectedly observed because at 50 °C decomposition of the residual anhydride was not complete in the 60 min total reaction time. The anhydride eventually decomposed during the distillation due to the presence of isopropanol, resulting in an equivalent of isopropyl ester **14** and benzoic acid (Figure 5). The isopropyl

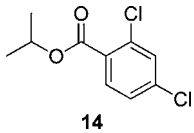

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Figure 5. Isopropyl ester impurity generated from anhydride decomposition.

ester was a liquid, so this impurity was easily purged, and the residual benzoic acid as the free acid was easily purged in the final crystallization.

To reduce the anhydride content prior to the extraction, the temperature was raised to 65 °C and the acid chloride equivalents were lowered to 1.2 for the second day as shown in Table 4. These conditions were a significant improvement as very low levels of anhydride entered the extraction, and residual sulfonamide levels were 0.50 and 0.52 HPLC area % respectively for days 2 and 3. Unfortunately, on day 4, the acid chloride pump failed for the first 25 min of the run before being restarted. This caused a buildup of the starting sulfonamide in the system, resulting in higher levels of compound **1** in the extraction product for the day (2.50 HPLC area %). On day 5 in an effort to reduce the acid chloride necessary for reaction completion, the equivalents were lowered to 1.15, and the residence time per CSTR was increased to 45 min. Overall, these conditions were less successful with levels of starting sulfonamide **1** above 2.0 HPLC area %. On day 6, the intermittent flows were increased to 10 min, providing 10 min aging time in CSTR 2, but this resulted in little improvement. Days 7 and 8 examined the same 45 min residence time and 7 min intermittent aging time in CSTR 2 but with increased acid chloride (1.2 equiv). This resulted in the necessary improvement in reaction completion (0.46 HPLC area % **1** for day 8), but to increase total mean residence time for reduction of anhydride an additional CSTR was added. τ of 60 and 45 min per CSTR were examined with 3 min intermittent flows between CSTRs. These conditions resulted in residual sulfonamide **1** below 0.5 HPLC area % and amidine **7** near 0.3 HPLC area %.

Upon completion of development work, the conditions examined generated similar results on days 8 and 10 from the perspective of residual starting material and amidine **7**. The levels of anhydride were higher for the two CSTR reaction run on day 8 contributing to the higher total related substances (TRS) exiting the reactor because of the 90 min τ with two CSTRs compared to 135 min τ with three CSTRs. τ for the extraction unit operation was sufficient to decompose the anhydride, resulting in nearly equivalent crystallization feed streams. Due to the importance of high purity in the final product, the three-CSTR system was chosen to ensure anhydride would be consumed during the reaction.

To help understand the importance of this choice, consider the design equation for ideal equal-sized CSTRs in series operating at the same temperature, conducting an irreversible first-order reaction and assuming that the volumetric flow rate does not change with reaction, where conversion of reagent to product is equal to $1 - 1/(1 + \tau k)^n$. Here k is the reaction rate constant, τ (or tau) is the mean residence time which is the same for all CSTRs in series, and n is the number of CSTRs in series.[22] If $\tau k = 6.0$, then conversion in CSTR 1 would be 86%. On day 8 conversion of **1** in CSTR 1 is 85.2%, corresponding to $\tau k = 5.7$. On day 10 conversion of **1** in CSTR 1 is 86.9%, corresponding to $\tau k = 6.6$. The day 8 experiment is the most representative of best conditions for continuous reaction using two CSTRs in series, and day 10 is the most representative using three CSTRs in series. The goal is 98% conversion, which corresponds to 0.5 HPLC area % of **1** in the reaction product solution. If one CSTR was used, $\tau k = 49$ would be required for the desired conversion. If reaction rate is constant and if the dominating rate-limiting step of the Schotten−Baumann reaction is pseudo-first-order, then this would mean that τ in CSTR 1 would need to be increased by a factor of about 8 times, from τ = 45 min to τ = 6 h, in order to achieve 98% conversion in a single CSTR. This would require a vessel about 8 times larger than the vessel size that was eventually utilized. However, one of the main goals of developing the continuous process is to use small, inexpensive, disposable glassware for the

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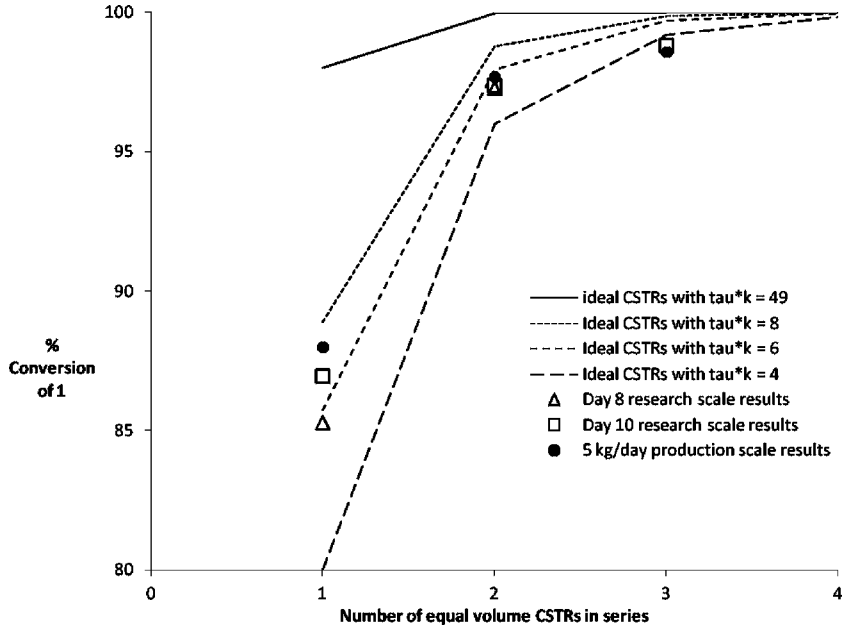

Figure 6. Conversion vs number of CSTRs in series, comparing ideal calculations to experimental data.

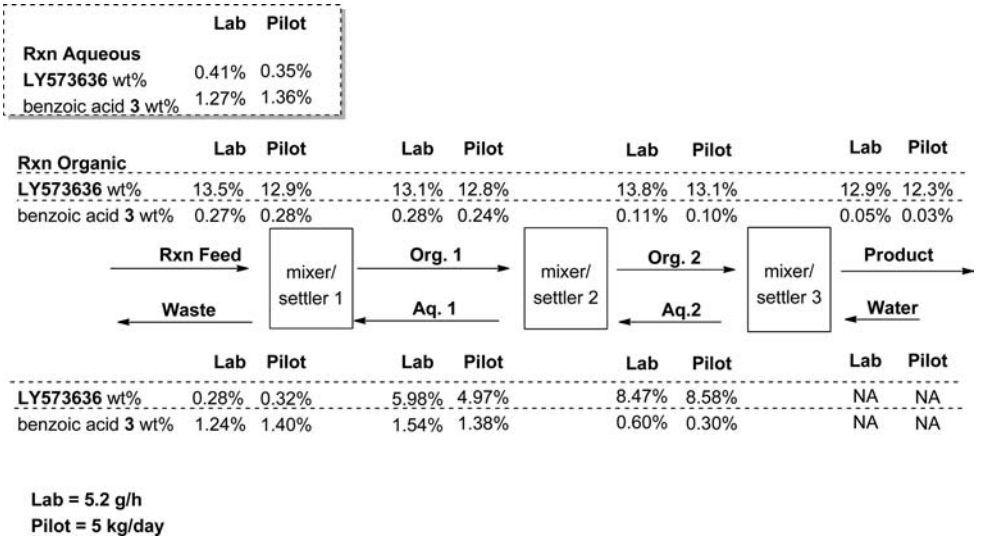

Figure 7. Steady-state data from countercurrent extraction on day 10 for the 5.2 g/h lab scale and the average values from the 5 kg/day scale-up.

reaction, separation, and crystallization operations. In contrast, using CSTRs in series and the same $\tau k = 6$, conversion would be 86, 98, 99.7, in CSTRs 1, 2, and 3, respectively. No doubt the kinetics of the continuous Schotten–Baumann reaction are much more complex than that of an elementary first-order reaction, but the purpose of this illustration is to explain why overall reaction time and volume for 98% conversion is less for CSTRs in series than a single CSTR, given a positive order reaction. The solid and dotted lines in Figure 6 show theoretical conversion as a function of the number of reactors in series for τk = 49, 8, 6, and 4, assuming equal volume, isothermal, ideal CSTRs running a first-order irreversible reaction. In addition, experimental data for days 8 and 10 for conversion of **1** in each CSTR are shown. Comparison of the experimental data points to those of the ideal model indicates that the Schotten–Baumann reaction in the CSTRs does not agree with elementary first-order rates, which is not surprising. However, it also helps to explain why we chose three CSTRs in series. The cost of adding the third CSTR is justified, but the cost of adding a fourth CSTR is probably not justified when τk is in the range 4–8 and the goal is 98% conversion. The scalability of this process is also highlighted in Figure 6 which shows that conversion in each CSTR was almost identical for the 5.2 g/h research runs and the 5 kg/day production run which is described later in this report.

Figure 7 shows the experimental results for continuous countercurrent liquid–liquid extraction collected on day 10. The benzoic acid **3** as the sodium salt was effectively removed in the aqueous waste and only 0.05 wt % was present in the product stream. Likewise, **LY573636·Na** was enriched in the product stream, and only 0.28 wt % was lost in the aqueous waste, translating to a 3% yield loss overall for the process. The mixers and settlers for the extraction performed as required, and this is especially evident in the third settler where the density difference is only 5% and the flow ratio of organic to aqueous phase is 7:1. The extraction was effective at removing

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Table 3. Distillation results from the final four days of processing (standard deviation in parentheses)[a]

	2-MeTHF wt %	isopropyl acetate wt %	isopropanol wt %	toluene wt %	water wt %	**LY573636·Na** wt %
extraction product	7.7 (0.4)	44.4 (2.3)	ND	24.6 (1.1)	10.4 (4.0)	12.8 (0.4)
1st add back	0.2 (0.0)	41.5 (1.5)	24.0 (0.7)	3.8 (0.4)	0.2 (0.0)	28.2 (2.0)
2nd add back	ND	42.9 (1.4)	26.7 (0.3)	0.4 (0.0)	0.1 (0.0)	27.2 (0.6)

[a]The data (one data point per day) from the final four days were most representative of the desired process both for reaction completion and optimized distillation pressure step-down sequence. Water for the extraction product was not tested; the reported wt % is based on the assumption that the remaining mass was residual water. The average and standard deviation results for each measurement are listed.

Table 4. Conditions for 5.2 g/h development run

	reaction conditions				crystallization feed[c]				isolated solids			
	# of CSTRs in series[a]	τ in each CSTR (min)/intermittent flow (min)	acid chloride **2** equiv	end of reaction TRS[b,c]	TRS	sulfonamide **1**	benzoic acid **3**	amidine **7**	TRS[d]	sulfonamide **1**	benzoic acid **3**	amidine **7**
day 1	2	30/7	1.30	8.55	5.74	0.33	4.17	0.29	0.32	0.01	0.09	0.03
day 2	2	30/7	1.20	6.19	5.04	0.50	3.08	0.29	0.23	0.02	0.02	0.03
day 3	2	30/7	1.20	2.57	2.13	0.52	0.72	0.34	0.25	0.02	ND	0.05
day 4	2	30/7	1.20	3.50	3.28	2.50	0.27	0.42	0.26	0.02	0.02	0.04
day 5	2	45/7	1.15	3.39	3.25	2.42	0.18	0.46	0.29	0.08	ND	0.04
day 6	2	45/10	1.15	3.12	2.96	2.23	0.17	0.38	0.30	0.09	ND	0.04
day 7	2	45/7	1.20	2.96	2.73	1.95	0.27	0.35	0.23	0.04	ND	0.03
day 8	2	45/7	1.20	2.31	1.19	0.46	0.32	0.30	0.19	0.03	ND	0.03
day 9	3	60/3	1.20	1.23	1.18	0.59	0.24	0.30	0.19	0.03	ND	0.03
day 10	3	45/3	1.20	1.37	1.26	0.45	0.30	0.31	0.20	0.03	ND	0.03
day 11	3	45/3	1.20	1.71	1.41	0.44	0.56	0.30	0.23	0.03	0.01	0.03
day 12	3	45/3	1.20	1.38	1.29	0.55	0.42	0.30	0.18	0.02	ND	0.03

[a]Temperature was 65 °C for all days with the exception of day 1 (50 °C). [b]Total related substances (TRS). [c]Run on 11 min Halo C18 method that does not provide separation of isomeric impurities. [d]Run on 35 min Discovery HS-C18 method that separates the isomeric impurities **11**, **12**, and **10** which are present in each lot of isolated solids at 0.10, 0.04, and 0.02%, respectively. For all reaction conditions it was expected these impurities would not be rejected under the reaction conditions and are representative of the purity of the starting materials.

inorganic salts as no buildup of solids was evident during the distillation and potency numbers for the final isolated solids were as expected. Most importantly, the extraction was effective at lowering the levels of the sodium salt of **3** which has appreciable solubility (1.20 wt %) in the crystallization feed, but not in the final crystallization solvent system (0.06 wt %) so this impurity would likely remain dissolved in the crystallization feed but precipitate during the heptane addition if not removed by extraction. On day 11 the effects of poor agitation in the extraction mixers were also examined with no deleterious effects. For the final day of the run, doubling the fresh water flow in the extraction resulted in a slightly lower yield of product but no measurable improvement in the benzoic acid removal.

For each of the 12 days the extraction product was concentrated to develop the pressure step-down sequence that would become the automated program for the larger-scale campaign. Three concerns for the distillation are the levels of water and toluene entering the crystallization and the ratio of **LY573636·Na**/isopropyl acetate/isopropanol. As mentioned previously, the product has high water solubility, and water entering the crystallization was shown to significantly impact recovery and impurity profile. The product also has poor solubility in toluene so residual levels were monitored to ensure that toluene would not potentially cause precipitation in the crystallization feed. Experimental data from Karl Fischer analysis and gas chromatography were collected to evaluate the process efficiency and ensure that the second solvent strip and add-back was necessary and also sufficient to achieve the desired crystallization feed composition. As seen in Table 3 the first add-back results in a solvent composition that was higher in toluene than desired, but water was already effectively removed. Once the material was concentrated to a foam and the second add-back was performed, toluene and water levels are both sufficiently reduced.

For the crystallization, a two-MSMPR system was utilized where a 27 wt % product stream in isopropyl acetate and isopropanol was added concurrently with 10 vol of heptane to a seed bed of **LY573636·Na** at room temperature. For this 5.2 g/h campaign, the seed bed was generated during batch startup by self-seeding with one residence time volume in the first MSMPR and allowing the seed bed to stir overnight. Once the seed bed was in place, flows were started, and the vessels ran as typical MSMPRs with no external seeding. Secondary nucleation likely dominated generation of new particles because the MSMPRs ran at low supersaturation. Intermittent pumping with a frequency of once every 3 min was utilized to transfer material between MSMPRs and to the filter. Due to the air flow in the fume hoods, there is a possibility the tubes and pumping mechanisms forwarding slurry out of each MSMPR could be cooler than the vessel; thus, a solubility study examining 15−25 °C was conducted. As expected, there was little temperature dependence with the solubility changing from 0.40 to 0.41 wt %, indicating fouling from crystallization in the transfer zone was a low risk. By definition, there will always be some degree of supersaturation in each MSMPR operating at steady state, or else crystallization would not occur; however, supersaturation was expected to be higher in MSMPR 1 because all of the antisolvent is added to that stage. This was verified experimentally as samples from MSMPR 1 showed 41%

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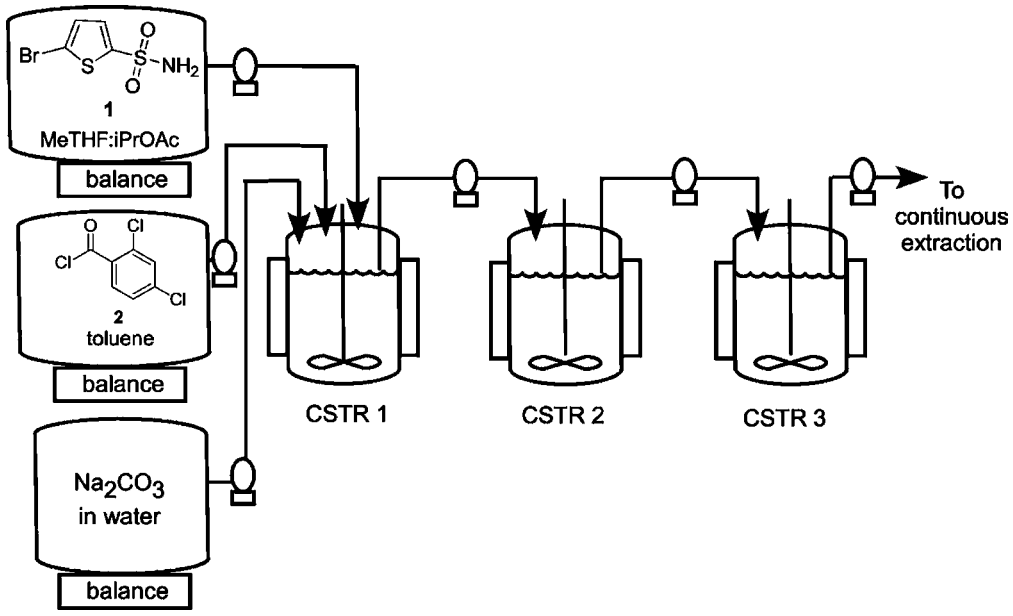

Figure 8. CSTR train used for Schotten–Baumann continuous reaction.

relative supersaturation and MSMPR 2 showed 8% at steady state.[23] The 5.2 g/h MSMPR crystallization ran with 60 mL volume in each MSMPR and 0.61 mL/min slurry flow for 10–12 h/day for 12 days without plugging or fouling. Finally, carbon treatment was a key component of all previous batch and continuous efforts to synthesize tasisulam due to the formation of colored impurities during the reaction. The Schotten–Baumann conditions generated no significant color beyond color present in the starting sulfonamide, and no carbon treatment was necessary.[24]

As shown in Table 4 the 12 lots of tasisulam that were isolated during the 5.2 g/h development campaign highlighted the robustness of the process and the ability of the extraction and crystallization unit operations to serve as effective impurity rejection points. In total, 273.0 g[25] of tasisulam were produced over a cumulative flow time of 120 h in 90% yield. Total impurities in the API ranged from 0.18 to 0.32 HPLC area % over the course of the run.

For the reaction, the run highlighted the importance of driving the reaction to completion and allowing sufficient time for anhydride **4** to decompose such that the resulting benzoic acid **3** could be removed during the extraction. Otherwise, the anhydride **4** would decompose in the distillation, forming a new impurity (isopropyl ester **14**) and placing a heavier burden on the crystallization. The robustness of the process also played an important role in the entire development run and demonstrated how equipment failures could easily be handled and with timely corrections no impact on the product was observed. With only a diptube to govern liquid levels in the extraction, regular manual adjustments were needed to control the research-scale flows. Therefore, gravity decanters were utilized for scale-up to 5 kg/day scale.[26] In general, a potential disadvantage of gravity decanters is that solids can accumulate in the bottom of the heavy phase over time if there are any insoluble species but that was not an issue for this process and once interface levels were set, gravity proved to be very reliable. The utilization of solvent exchange with a rotary evaporator also proved to be very powerful, removing toluene and water to the necessary levels and because the material was stripped to a foam, the add-back solvent was added at the exact ratio that was required for the subsequent crystallization ensuring consistent feeds. Again, normally solvent exchange with strip to dryness in not considered a legitimate option for commercial manufacturing, but it is for this API as discussed in this report. In summary, the 12-day campaign demonstrated not only a very robust process but a reliable equipment set. Overall, most days of the reaction operated under less than ideal conditions due to the optimization activities involved with the reaction. Nevertheless, all material was forward processed, and the extraction and crystallization provided the impurity rejection necessary to generate **LY573636·Na** with the required purity profile.

The conditions of day 10 in Table 4 were selected as the basis for scaling up the continuous process. It is important to note that most of the design and development work on this chemistry used for the continuous process was done through batch research-scale experiments. This includes route selection, screening for reagents, solvent type, Schotten–Baumann conditions, concentrations, temperatures, reaction rates, reagent addition order and rates, thermodynamics and safety testing, phase transfer catalyst, effect of mixing rate, impurities generated, fate of known impurities in starting materials, analytical, stable hold points, solubilities, densities, visual observations of phases, all methods and materials for isolation, and corrosion testing on materials of construction. The continuous flow experiments at research scale served to verify that heat and mass transfer rates were sufficient in the selected equipment types so that results matched expectations from the batch experiments, and to quantify final concentrations of key impurities through a continuous process which is difficult to predict by batch experimentation.

5 Kilogram/Day Run (Equipment). Several important observations from the 5.2 g/h development run resulted in improvements in the equipment set for the 5 kg/day demonstration. A schematic diagram of the 3 CSTRs-in-series reaction train used for Schotten–Baumann continuous reaction is shown in Figure 8. In order to minimize worker exposure to the cytotoxic product, a second smaller set of 10 mL transfer zones was utilized to serve as an automated method to pull the

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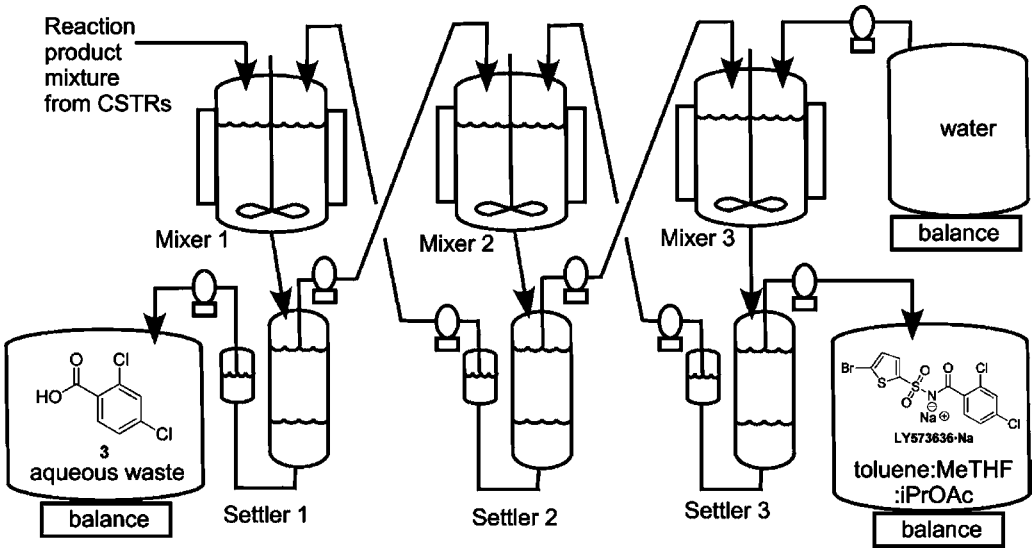

Figure 9. Mixer–settlers in series train used for continuous countercurrent liquid–liquid extraction.

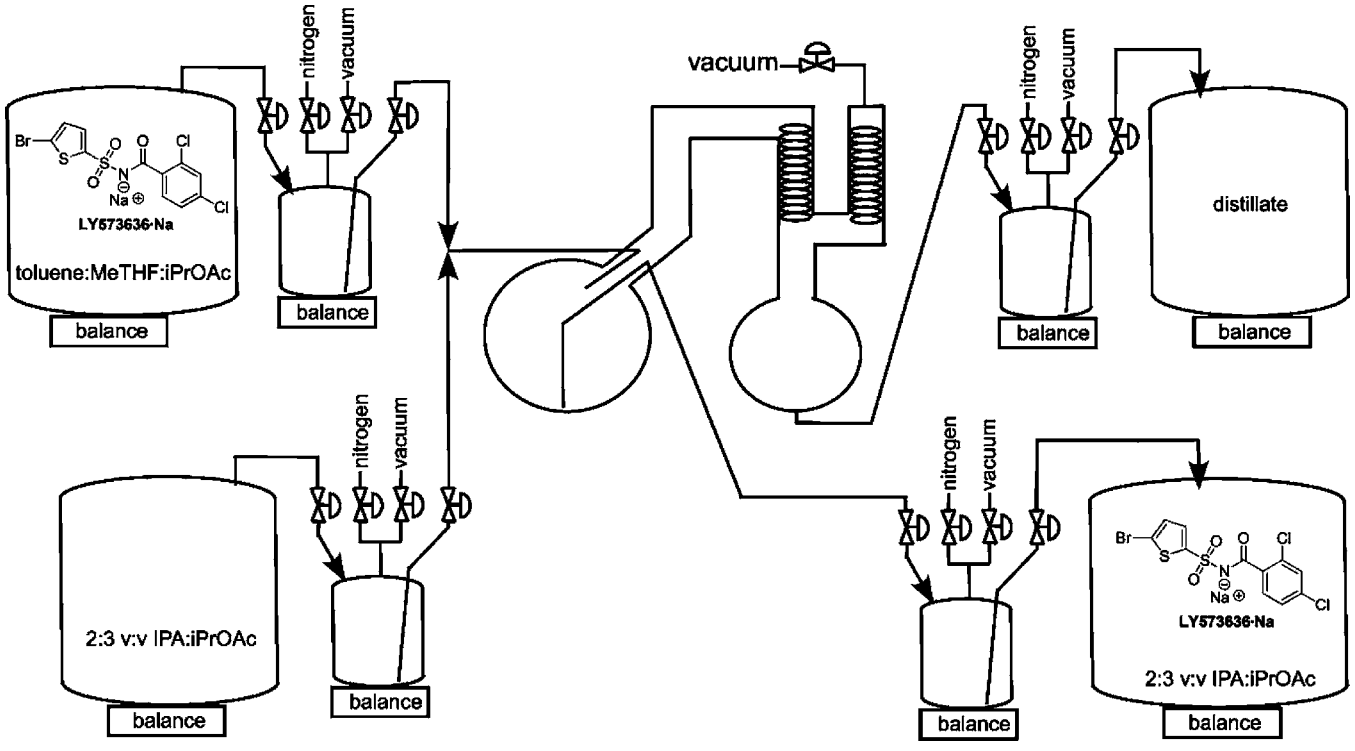

Figure 10. Automated repeating semi-batch solvent exchange with strip to dryness in rotary evaporator.

analytical samples from each reactor. Redundancy was used for measurement of all temperatures and all mass flow rates. The reaction feed solutions were generated in a batch stirred vessel and then transferred to an 8-gal Hastelloy C vessel (acid chloride **2**), a 16-gal stainless steel vessel (sodium carbonate) and a 20-gal Hastelloy C vessel (sulfonamide **1**). In the entire process including reaction, extraction, solvent exchange, and crystallization, most feed streams were delivered with pressurized feed tanks, coriolis mass flow meters, and automated control valves for the 5 kg/day process, as opposed to the dual syringe pumps that were used for the 5.2 g/h scale research runs. A dual glass syringe pump[27] was utilized with 50 mL syringes for the acid chloride feed stream due to a relatively low flow rate. Mass flow rates of all feeds and product solutions were measured by change in weight vs time on data logging floor scales.

A schematic diagram of the three-stage countercurrent mixer–settlers used for continuous liquid–liquid extraction is shown in Figure 9. Three **5** L round-bottom glass flasks were used for mixers and 3 L flasks for the main separating volume of the gravity decanters. Coalescing screens were used between the mixers and settlers, made from Hastelloy wire mesh packed inside Teflon tubing. Peristaltic pumps were used to transfer the aqueous and organic phases out of the gravity decanters.[28] An FMI pump was used for the delivery of water into the third mixer from a 16-gal stainless steel vessel.

Parallel surge tanks were utilized after the continuous extraction so while one tank of extraction product was feeding

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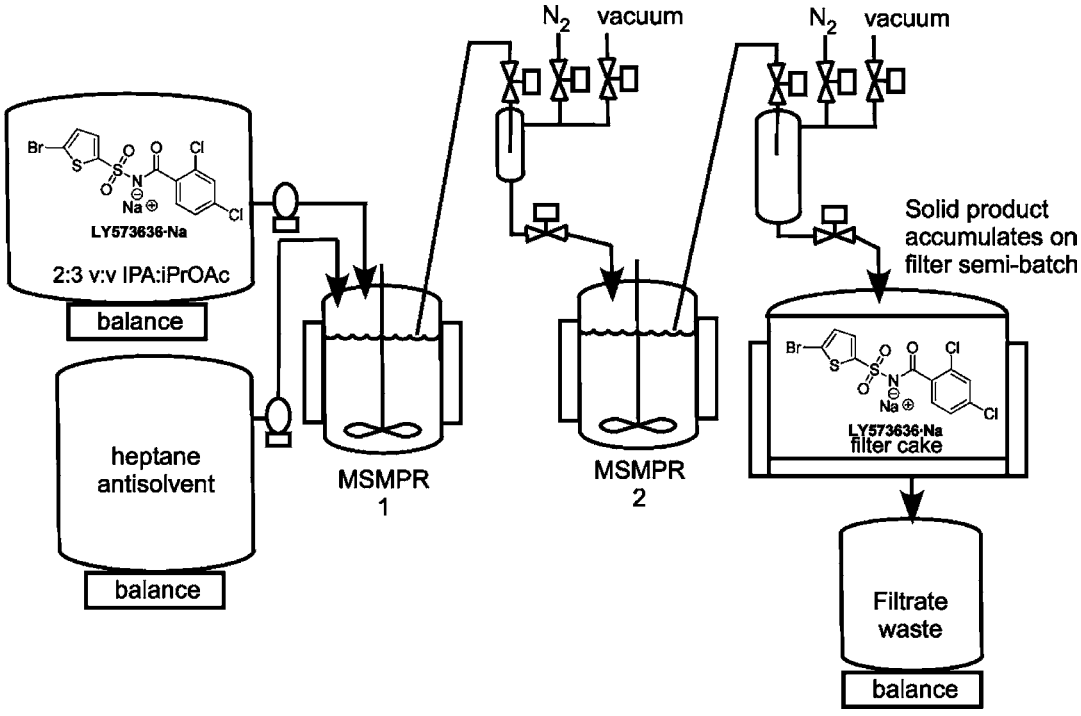

Figure 11. MSMPR cascade used for continuous crystallization and semibatch filtration of API.

the distillation a second tank was collecting from the extraction. The utilization of parallel surge tanks ensures that the material balance and quality of the product stream can be checked prior to committing the material to the subsequent unit operation.

For the distillation, the step up in scale required the change from a 3 L flask for the Buchi rotary evaporator to a 20 L flask. A schematic diagram of the intermittent flow, automated sequenced batch solvent exchange distillation can be seen in Figure 10 which was the most automated unit operation in the process train, controlled by DeltaV. Automated valves and pressure swing vessels on data logging balances accurately and precisely controlled all intermittent flow masses and timing into and out of the rotary evaporator.

Since the product was a nonsterile API for parenteral use, procedural changes were incorporated for the crystallization to ensure that the continuous process could generate material with all the necessary quality attributes including microbial and endotoxin control. A schematic diagram of the MSMPR cascade used for continuous crystallization of the API is shown in Figure 11. Two MSMPRs were utilized just as in the development work, but the first MSMPR was a 12 L flask while the second was a 22 L flask. The transfer zone from the second MSMPR to the filter was increased to 3 L in size so large transfers could be sent to the filter every 30 min to ensure a uniform cake that could be washed without channeling. Running with heptane on this scale led to safety concerns about static electricity and to this end the heptane feed line into the tank was changed to stainless steel rather than Teflon and care was taken to ensure the entire system was inert and properly grounded. The isolation sequence was also slightly modified to contain three filters: a 6 L glass pressure filter and two 0.41 m single plate filters. Due to the cytotoxic nature of the product, the glass pressure filter would allow isolation and drying of a smaller batch, approximately 500 g. This amount lessened worker exposure concerns but was still sufficient for analytical testing and for formulation development. A small analytical sample would be taken from the material isolated on the larger filters and then the product would be dissolved off the filter with acetone and sent to waste.

A solvent run was performed on all four unit operations utilizing solvent feeds that were as close as possible to the actual feeds. This was an important opportunity to test the equipment, automation and material balance. No issues were observed and a material balance of 99.6% was observed for the reaction/extraction, 97.3% for the distillation and 99.2% for the crystallization.

5 Kilogram/Day Run (Results). The 5 kg/day processing plan was designed for zero startup or shutdown transition waste. Continuous reaction, extraction, and crystallization were all started and shut down semibatch, and the solvent exchange used automated repeating semibatch cycles for the entire campaign. This was one of the benefits of selecting stirred vessels, or stirred vessels in series, as the technology choice for the unit operations. Surge vessels were used at the outlet of continuous extraction and the outlet of continuous solvent exchange, which also made startups and shutdowns easier because it decoupled the unit operations. During batch start up of the reaction, a higher level (0.50% compared to 0.30%) of the acyl sulfonamide impurity **5** was generated compared to the continuous reaction, due to side reaction of sulfonamide **1** with isopropyl acetate during batch heat-up time and during the 1 h controlled addition of **2**. During the first 50 min of the slow addition there was less than 1 equivalent of **2** relative to **1** in the reactor, which is typical of standard batch reaction with slow addition of one reagent. In contrast, during the continuous reaction at steady state there is always excess acid chloride relative to **1** in the reaction zones which results in a more favorable impurity profile with respect to impurity **5** via the continuous reaction. The sodium salt of **5** has very good water solubility so this was not an issue from an impurity profile perspective but could contribute to a lower yield if prolonged heating was encountered. This highlights the subtle difference

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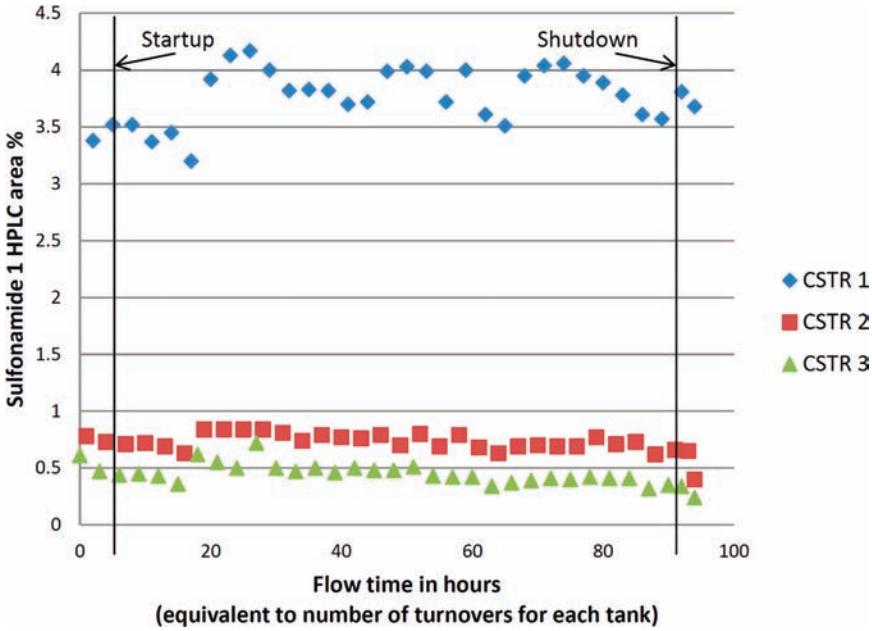

Figure 12. Comparison of starting material conversion in CSTR 1, 2, and 3.

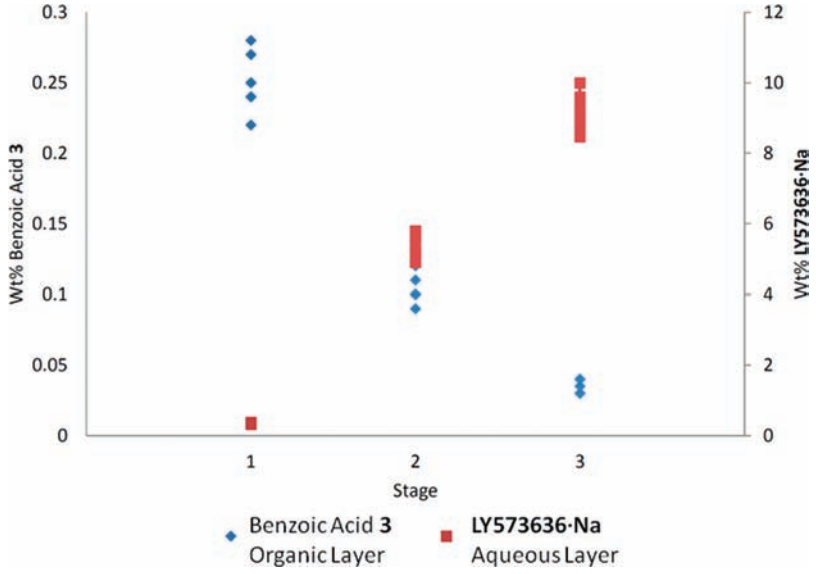

Figure 13. Effectiveness and consistency of extraction unit operation (16 data points collected for each stage).

in impurity profile between batch and continuous reaction in CSTRs which is difficult to predict before actually running in CSTRs. The important lesson was that the mixing time of the sulfonamide and sodium carbonate solutions prior to the start of the acid chloride feed should be minimized as this was not a stable hold point. This information also highlighted the quality control benefit of running this chemistry in a continuous manner and the potential difficulty that could arise from running these conditions on larger scale in batch mode as the time required to heat the solutions would increase with each step-up in scale. During semibatch startup of the extraction, a feed of fresh water was charged to the second and third stages. The only consequence to the startup material from this protocol was a slightly lower initial product weight percent as this startup material effectively saw two fresh water washes. The crystallized product was separated into 5 lots, a 12 h start-up transition lot, three 24 h steady-state lots and a 12 h shutdown transition lot. The two MSMPR crystallizers were started in batch mode using 2 g seed. After batch startup, no additional seed was used during the 20 kg continuous crystallization run and therefore seed loading was only 0.01%, which is one of the advantages of continuous versus batch crystallization in general.

During the campaign, agitation was lost for 15 min in the first reaction CSTR resulting in 15 min of the upper organic phase flowing out of the CSTR at about twice the steady-state flow rate resulting in the accumulation of aqueous phase in the first CSTR. Once agitation was restarted a 5 °C temperature spike occurred because a temperature gradient developed when there was no mixing. The heating mantle on the bottom of the vessel was heating the stagnant aqueous layer in the flask, but the control thermocouple was up in the stagnant organic layer, therefore the thermocouple detected the higher temperature once mixing restarted, but this did not have a negative impact on the impurity profile indicating the robustness of the

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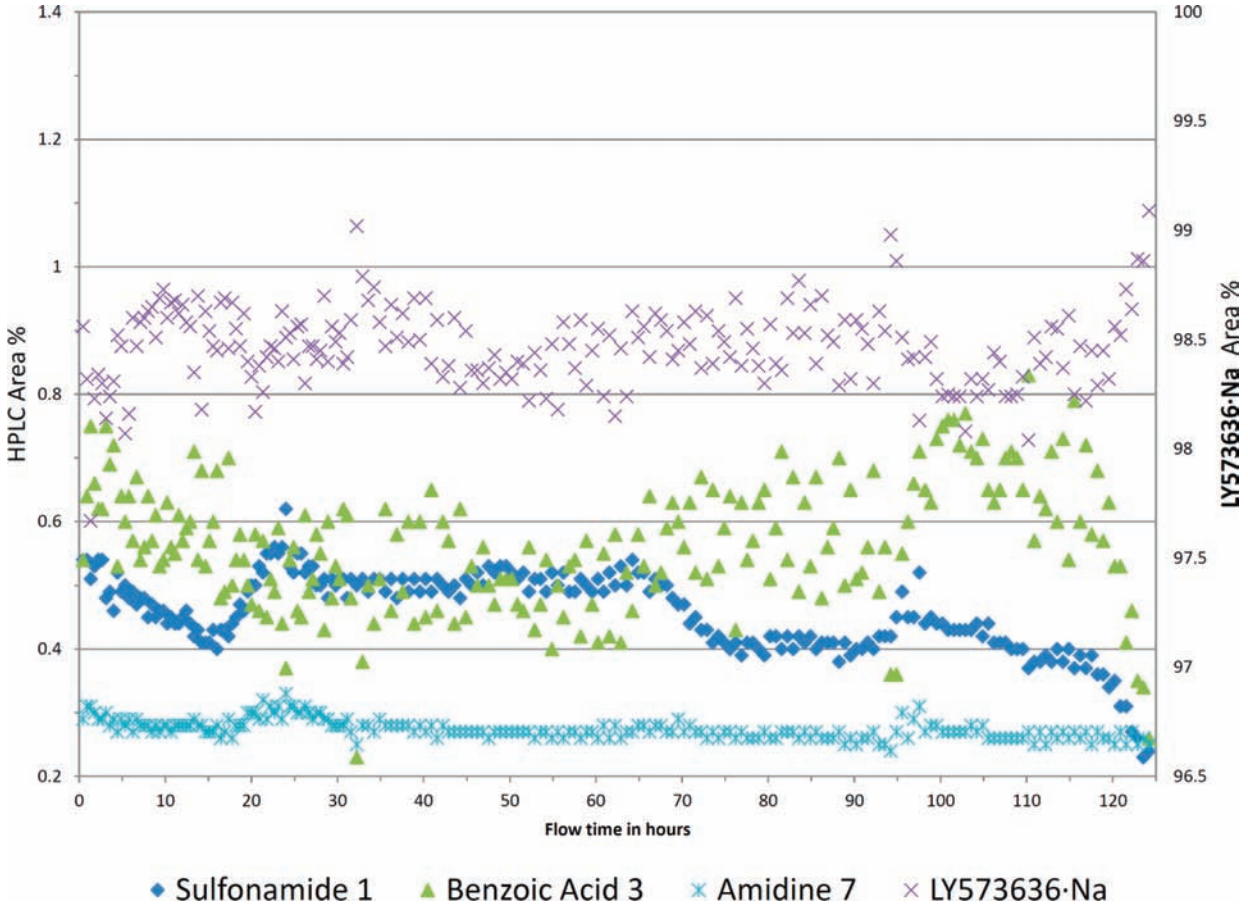

Figure 14. HPLC data from settler 3 collected from the autosampler.

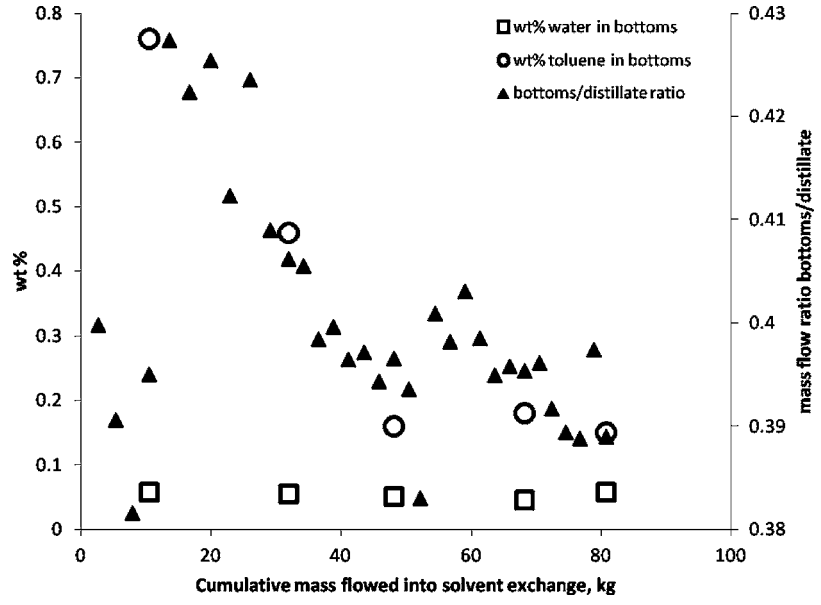

Figure 15. Residual water and toluene levels in product solution after solvent exchange and mass flow trends for solvent exchange.

reaction. Feed rates and temperature were very steady throughout the process, all three flows were ±0.5% of the desired set point and the temperature in each of the CSTRs was within 1 °C of the 65 °C set point with the exception of the spike mentioned above. As seen in Figure 12, a constant level of conversion was observed leaving CSTRs 2 and 3 and most notable the startup and shutdown materials also show very similar conversion. These numbers correspond to 87% conversion in the first CSTR, 97% in the second and >98% in the final reactor resulting in residual HPLC area % of the sulfonamide **1** of <0.5%. Additionally, the key impurity amidine 7 was always observed within a narrow range between 0.24 and 0.30 HPLC area %, levels the crystallization had already demonstrated the ability to reject.

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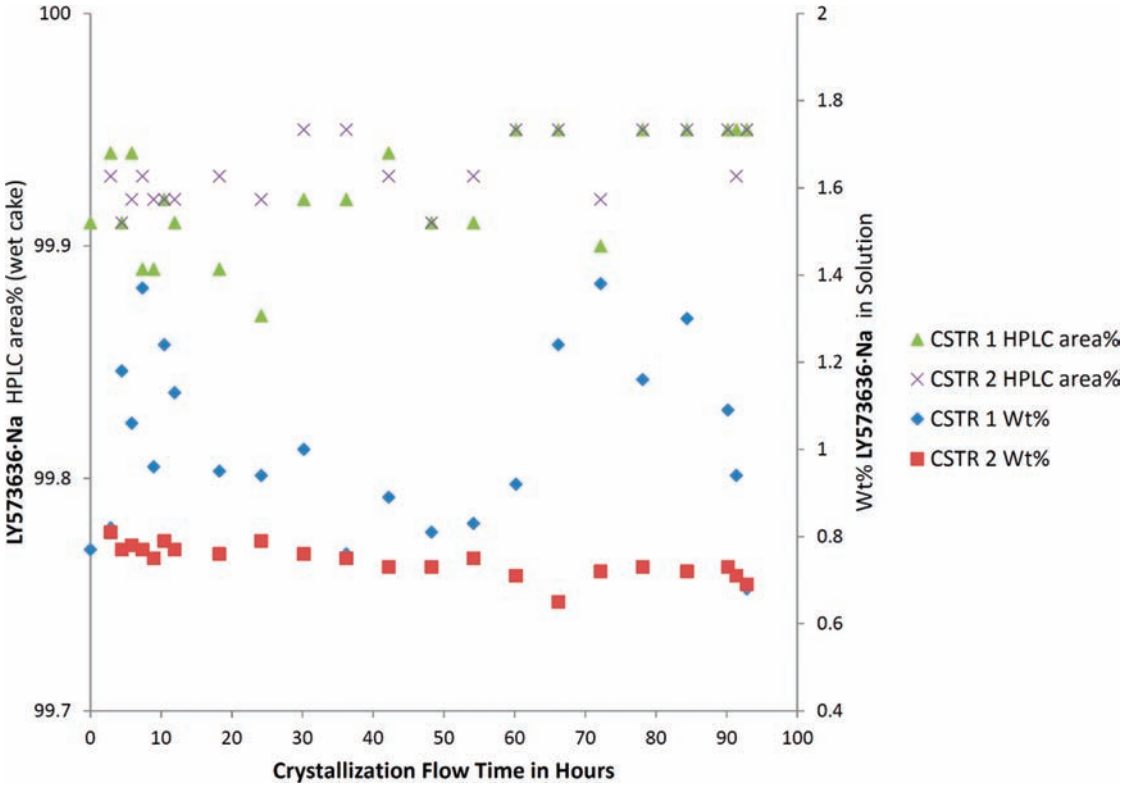

Figure 16. Comparison of wet cake purity and wt % **LY573636·Na** in filtrate.

Table 5. Purity of feed streams for crystallization and yields and purity of isolated solids[30]

Crystallization Feed Solution					Isolated Solids				
Feed solution (kg)	TRS[1]	Sulfonamide 1	Benzoic acid 3	Amidine 7	kg	TRS[2]	Sulfonamide 1	Benzoic acid 3	Amidine 7
9.82	1.16	0.49	0.22	0.30	5.47	0.50	0.02	ND	0.02
13.71	1.09	0.53	0.23	0.27					
1.91	1.09	0.53	0.23	0.27	0.47	0.51	0.02	ND	0.02
4.64	1.09	0.53	0.23	0.27	4.35	0.51	0.02	ND	0.02
13.56	1.05	0.49	0.25	0.28					
6.17	1.05	0.49	0.25	0.28	5.81	0.51	0.02	ND	0.02
14.44	0.97	0.42	0.28	0.27					
1.92	0.97	0.42	0.28	0.27	0.46	0.51	0.02	ND	0.02
3.26	0.97	0.42	0.28	0.27	3.27	0.50	0.02	ND	0.02
7.93	0.90	0.35	0.23	0.27					

[1]Run on 11 min Halo C18 method that does not provide separation of isomeric impurities. [2]Run on 35 min Discovery HS-C18 method that separates the isomeric impurities **11**, **12** and **10** which are present in each lot of isolated solids at 0.10, 0.32 and 0.03% respectively.

HPLC samples pulled from each of the settlers showed a very efficient and robust process as seen in Figure 13. While there was some fluctuation in the data, the two most important numbers, benzoic acid levels in the organic product (stage 3) and **LY573636·Na** lost to the aqueous (stage 1), were very steady. For example, in Figure 13 it looks like there is one data point for **LY573636·Na** concentration in the stage 1 aqueous equal to about 0.3 wt %, but this is actually 16 data points on top of each other in the figure each collected 4−8 h apart during the run. As expected, levels of benzoic acid were high in the incoming organic but grew successively lower with each stage. Similarly, the **LY573636·Na** aqueous concentration in stage 3 was high, but this material was partitioned into the organic before exiting the system in the aqueous waste. Samples were pulled using an automated sampling and dilution system from the third settler organic layer representing the same material that was being fed to the extraction product can.[29] As can be seen in Figure 14 the process delivered a very consistent product stream throughout the run, and these data exemplify the robustness of the process including the startup and shutdown material that was of the necessary purity for forward processing. The rationale for what appears to be a trend in the

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levels of sulfonamide **1** cannot entirely be explained, but the slight increase observed starting at 20 h coincides with the loss of agitation in the first reaction CSTR, and the decrease after 60 h might be explained by change in feed lot half-way through the run. Overall, the robustness of the crystallization was more than adequate to reject the impurity levels that were observed. For the entire campaign an average of 0.32 wt % of **LY573636·Na** was lost to the aqueous layer of the extraction, accounting for 3% yield loss for the process.

During the campaign, the distillation unit operation in the 20 L Buchi encountered some minor scale-up issues. For the first two lots, the toluene level in the precrystallization feed stream was higher than had been observed in the 5.2 g/h run resulting in a slightly lower weight percent feed than anticipated. This occurred because the flask fill volume was increased to 28% and the larger-scale flask has lower heat transfer surface area per unit volume, resulting in a thicker layer of solids on the heat transfer surfaces when the process is scaled up. While water removal was still effective, the level of toluene was below the threshold of 1 wt % but was higher than desired (Figure 15). To improve the operation for the second lot, the bath temperature was changed to 60 °C which provided improvement, but the toluene level was still higher than desired. For the remainder of the run, the initial Buchi charge was lowered to a 23% fill volume, generating similar residual solvent levels compared to what was observed during development. In addition to residual levels of water and toluene in the solvent-exchanged product solution, Figure 15 also shows the mass flow ratio bottoms/distillate, where "bottoms" is the product solution exiting the evaporator flask and "distillate" is the stripped solvent exiting the distillate receiver flask. All solvent exchange data in the Figure 15 is plotted as a function of cumulative mass flow out of the unit operation, which is analogous to plotting as a function of cumulative operation time. As we would expect, the trend of decreasing residual toluene is similar to the trend of decreasing bottoms/distillate ratio. It is also worth noting that the earliest samples have lower mass flow ratio bottoms/distillate because the startup material was light in product before the extraction reached steady state so the API loading was lower.

Figure 16 and Table 5 show results for the 88 h continuous crystallization run. A τ of 1 to 3 h is common for MSMPRs, and typically 7−10 τ is needed to reach steady state in MSMPRs.[7,8] τ for each MSMPR in this study was 90 min, therefore time to steady state could be as long as 15 h for just the first MSMPR. From an R&D perspective, this required long experimental run times in the laboratory. From a business perspective, it also highlights the importance of proving that critical quality attributes are achieved during startup transition, because it would not be desirable to divert up to 24 h of product during startup transition. The goal was to proceduralize semibatch startup and shutdown and quantify product quality during the transition to steady state and to prove that all API met critical quality attributes. For the crystallization, the larger transfer zone from the second MSMPR to the filter was very effective; the less frequent and larger slurry transfers helped to maintain cake uniformity and ensured a consistent wash could be applied. Analytical samples were pulled from both MSMPRs to monitor the wet cake and mother liquor as seen in Figure 16, which exemplifies several things. First, it shows the level of consistency of **LY573636·Na** concentration in the liquid phases in both MSMPR crystallizers over time for the 88 h continuous run. The scatter in the data for the first MSMPR can be attributed to the sample point location being too close to where feed solution flowed into the tank. Second, as we would expect the **LY573636·Na** concentration in solution in MSMPR 1 was higher than in MSMPR 2. All of the antisolvent is added to MSMPR 1, and thus MSMPR 2 runs closer to full desupersaturation than MSMPR 1 at steady state. Third, wet cake HPLC area % for samples pulled from both MSMPR 1 and MSMPR 2 were very high in product area % for the entire 88 h continuous crystallization run. Area % product was in the range 99.85% to 99.95% for solid samples pulled from MSMPR 1, and 99.90−99.95% for solid samples pulled from MSMPR 2 exemplifying the quality control advantage of steady-state continuous operation. Custom-built autosamplers were used to pull slurry samples at regular frequency from both MSMPRs for containment, product quality, and industrial hygiene reasons.

Comparing this to equilibrium solubility in each stirred tank, the relative supersaturation levels were roughly 55 ± 25% and 9 ± 5% in the first and second MSMPR, respectively.[23] By definition, MSMPR continuous crystallizers operate with some positive degree of supersaturation at steady state, otherwise, crystallization would not occur. As a result, yield would be 0.24% higher if the crystallization reached equilibrium when performed in batch mode.

During the course of this 88 h crystallization, solids did build up but not to the extent that it was necessary to stop processing and clean the MSMPRs. On one occasion, a small amount of this material on the vessel walls did break free and become lodged in the 1/4 in. diameter flow restriction to the transfer zone. This was easily cleared without breaking containment before the next transfer so there was no impact on the overall process and this piping restriction was subsequently removed from future equipment setups. As in any continuous crystallization process in manufacturing, temporary shutdowns and restarts would be scheduled periodically to clean out sequestered solids. This campaign showed that continuous run time between scheduled shutdowns could be more than 88 h.

Four lots of solids were isolated and then washed with an isopropyl acetate/isopropyl alcohol/heptane mixture on the 0.41 m plate filters. Analytical samples were taken of the wet cake and then the wet solids were dissolved with acetone and sent to waste because the main purpose of this campaign was to generate information, not material. In order to determine the process yield, samples were taken of these waste solutions and analyzed for weight percent product, and total cumulative mass of the waste solution measured to determine total mass of product that had accumulated on the single plate filter before redissolving for disposal. For a more thorough analytical analysis, approximately 500 g were isolated on a small pressure filter twice during the campaign. In total, 19.53 kg were isolated for an 84.9% yield and an average throughput of 222 g/h, which is a 43× scale-up of mass flow rates from research-scale continuous runs. For the entire process the average filtrate concentration of **LY573636·Na** was 0.72 wt %, accounting for a 9% yield loss.

Solid samples from all six batches passed color and clarity tests and had excellent purity as seen in Table 5. The overall impurity level was controlled and was as expected. A significant fraction of the impurity load was due to the isomeric impurities **11**, **12**, and **13** in the purchased reagents that the extraction/crystallization processes were known to not purge. The main process impurities, sulfonamide **1**, benzoic acid **3**, and amidine **7** were consistently at or below 0.02 HPLC area % for all the batches. Additionally, the two samples that were isolated on

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smaller scale passed the endotoxin, mold/yeast, and microbial tests to demonstrate the robustness of the process and its ability to generate material of the necessary quality. These results also compare very well with the development results run on day 10 (Table 4) that were the basis for the 5 kg/day campaign, when crystallization feed showed 0.46 HPLC area % of sulfonamide **1** and 0.30 HPLC area % of the amidine **7**, resulting in isolated solids with 0.03 HPLC area % of each of those same impurities. Achieving the same product purity and yield at two scales that span 43× difference in mass flow rates exemplifies that this is a scalable process, and it also proves that the 5.2 g/h experimental results are predictive of 5 kg/day scale performance. This is important because proven acceptable range (PAR) studies would be performed at the 5.2 g/h scale to minimize material requirements.

The total material balances for all of the unit operations during the run were very good with the coupled reaction/extraction delivering 100.0% material balance, the distillation delivered 99.3% material balance, and the crystallization delivered 98.8% material balance. The process mass intensity (PMI) for the continuous process as described here was 25, exemplifying the efficiency of the process. This compares well to the impressively low PMI of the existing batch process with two isolations, which also equals 25. However, if the industry standard PMI calculations included mass of the cleaning solvents, then in this scenario PMI of the batch process for a small production campaign could be significantly higher than PMI of the continuous process. Significant cleaning solvent would be used for the multiuse batch equipment to eliminate cross-contamination when the equipment is used to campaign a different cytotoxic compound, and this could require more time and solvent than the actual production of the API if the campaign is short. This concern is alleviated by the continuous process described herein.

■ CONCLUSIONS

Continuous Schotten−Baumann conditions to deliver **LY573636·Na** were successfully utilized for proof of concept studies, 5.2 g/h continuous runs and a 5 kg/day continuous 96-h campaign to produce 19.5 kg of cytotoxic **LY573636·Na** in laboratory fume hoods. Both scales showed a very robust chemical transformation, purification, and isolation. This work also highlighted the subtle differences in impurity profile for batch conditions when compared to the continuous run for the same Schotten−Baumann chemistry. Batch reaction conditions resulted in 0.50 HPLC area % acyl sulfonamide impurity **5** compared to 0.30% during the continuous reaction in stirred tanks in series, because of different kinetic regimes in batch compared to CSTRs. The reaction, extraction, distillation, and crystallization platform technologies were designed with scalability in mind and equivalent yield and purity was achieved at both scales. Extraction and crystallization were both essential to impurity control strategy. Product yield and impurity rejection in the extraction unit operation benefitted from countercurrent multistage separations which was enabled by continuous processing. Both continuous extraction and continuous crystallization benefitted from the quality control advantages of steady-state operation. The use of transfer zones allowed processing with intermittent flow and controlled liquid level in the vessels. Intermittent flow was needed for pumping slurries without plugging and for running the solvent exchange distillation in a rotary evaporator by stripping to a foam. Utilization of an automated Buchi rotary evaporator for the distillation provided a powerful advantage by generating a very consistent composition after the distillation, enabling consistent continuous crystallization. Some distinct advantages of this process were the reduction in the number of unit operations from the original two-step batch process including the use of only one solids isolation and drying operation. In addition, due to the portable, dedicated, "disposable" equipment set, the potential for cross-contamination was eliminated, and final cleaning requirements were reduced. The equipment set was so inexpensive that it was still economical even if used for only one API. This reaction, extraction, distillation, and crystallization equipment was small enough that it was contained in laboratory hoods, which minimized potential for operator exposure to the cytotoxic API. The key quality attributes were consistent with those of the previous batch route; equally important from a quality perspective, the startup and shutdown material was well within the desired specifications, alleviating the need to divert product during startup and shutdown transitions.

■ EXPERIMENTAL SECTION

Materials. Starting materials and reagents were purchased commercially and used without further purification. All reaction feeds were filtered through a 5 μm filter before charging to feed cans to keep solids from plugging the flow restricting trims and needles of the automated control valves.

Continuous Flow Reaction Procedure. Reagent solutions were prepared batch. Sodium carbonate (13.20 kg, 124.54 mol, 2.2 equiv) was dissolved in purified water (137.0 kg) in four batches in a 50 L stirred flask resulting in an 8.8 wt % solution with a density of 1.09 g/mL. The starting sulfonamide **1** (13.69 kg, 56.54 mol) was dissolved in 2-MeTHF (17.81 kg) and isopropyl acetate (90.30 kg) in three batches in a 50 L stirred flask resulting in a 11.24 wt % solution with a density of 0.93 g/mL. The acid chloride **2** (14.2 kg, 67.8 mol, 1.2 equiv) was diluted in toluene (47.4 kg) in four batches in a 50 L stirred flask resulting in a 23.0 wt % solution with a density of 0.95 g/mL. Reagent feed solutions were transferred to feed vessels by vacuum, then pressurized to 10 psig in the feed vessels. Flow rates for the three reaction streams were set to 21.57 mL/min for the sulfonamide feed, 10.70 mL/min for the acid chloride feed, and 22.87 mL/min for the sodium carbonate feed. For the batch startup of the reaction, the first CSTR was filled with 2.407 kg of the sulfonamide solution and 2.977 kg of the sodium carbonate solution, and the reaction was then heated to between 63 and 67 °C. Once the desired temperature was reached, the acid chloride feed was started at the flow rate of 21.40 mL/min until 1.2 equiv had been added over 60 min.[31] The reaction was allowed to stir between 63 and 67 °C for 60 min before starting to pump out of CSTR 1. All three reagent feeds to CSTR 1 were simultaneously started at the feed rates setup at the start of the reaction. The three reaction feeds flowed continuously into CSTR 1 for a total of 94.5 h from startup until the beginning of the shutdown procedure. Shutdown was done semibatch, with CSTR 1 emptying, then CSTR 2, and CSTR 3 emptying at the same constant flow rates. During the course of the reaction a total of 12.75 kg (52.66 mol) of sulfonamide **1** were fed into the reaction. Over the course of 120 h a startup lot of product from settler 3, three steady-state lots, and a shutdown lot were collected from the extraction and kept separate through solvent exchange distillation by switching back and forth between the two parallel surge vessels between unit operations.

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For each automated cycle of the rotary evaporator, 4−5 kg of solution was pumped into the Buchi flask and concentrated by a programmed pressure decrease with a bath temperature of 60 °C. The bath temperature was held at 60 °C for the entire run and the streams heated as they flowed in and cooled as they flowed out. The pressure gradient began at 170 Torr for 4 min with step-down to 130 Torr for 4 min, 75 Torr for 4 min, 40 Torr for 8 min, and finally 30 Torr for 10 min. The resulting oil/foam was redissolved with a 3-vol[32] charge of 60/40 isopropyl acetate/isopropanol v/v. After the programmed time for dissolution, the distillation was started at 100 Torr for 4 min, 60 Torr for 4 min, 40 Torr for 5 min, and finally held at 30 Torr for 10 min. The resulting foam was dissolved in 3 vol of 60/40 isopropyl acetate/isopropanol v/v and then transferred to the feed can for crystallization. The MSMPRs were started by charging 1.38 kg of the isopropyl acetate/isopropanol feed solution to the first MSMPR. Ten volumes of heptane was then added over 95 min between 18 and 22 °C, the resulting mixture was seeded with 2 g of **LY573636·Na**, and the resulting slurry was allowed to granulate overnight. To this seed bed the solution of **LY573636·Na** was started at a rate of 14.3 mL/min, and the heptane was started at a rate of 40.2 mL/min. Pumping slurry from MSMPR 1 to MSMPR 2 was done by intermittent flow of 150 mL of slurry once every 2.76 min. Once the second MSMPR was full to one residence time (90 min), the transfer zone to the filter was started. Pumping slurry from MSMPR 2 to the filter was done by intermittent flow of 1.8 L slurry once every 30 min. The transfer zone was automatically rinsed with 50 g of the wash solvent (1.8:1.2:10 v:v isopropyl acetate/isopropanol/heptane) as part of the programmed sequence after each transfer and sent to the filter. Once approximately 4 kg of wet cake had been collected, the cake was washed (12 kg, 1.8:1.2:10 v:v isopropyl acetate/isopropanol/heptane).[33] Upon completion of the crystallization feed, flows were stopped, both MSMPRs were allowed to age for 90 min, and then the slurry was sent to the filter. A total of 6 lots of **LY573636·Na** (19.53 kg, 44.68 mol) were generated via these conditions for an overall yield of 84.9%. (^{1}H NMR (d_6-DMSO, 400 MHz): δ 7.53 (d, J = 8.4 Hz, 1H); 7.49 (d, J = 1.6 Hz, 1H); 7.35 (dd, J = 8.4, 1.6 Hz, 1H); 7.31 (d, J = 4.0 Hz, 1H); 7.14 (dd, J = 4.0, 0.8 Hz, 1H). ^{13}C NMR (d_6-DMSO, 100 MHz): δ 169.9, 148.7, 138.7, 132.9, 131.4, 131.0, 129.3, 129.2, 129.0, 126.6, 114.6.

■ ASSOCIATED CONTENT

Supporting Information

This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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(15) The precipitation of well-behaved solids during the reaction is not necessarily an issue for the continuous equipment set that will be utilized and will be covered in the crystallization discussion.

(16) Solids in transfer lines were observed in a pilot-plant scale batch campaign.

(17) neMESYS pumps were utilized for these additions: http://www.cetoni.de/englisch/products/syringepump_nemesys_technic.html.

(18) http://www.emerson.com/en-US/Pages/Default.aspx.

(19) Braden, T. M.; Gonzalez, M. A.; Jines, A. M.; Johnson, M. D.; Sun, W.-M. Reactors and methods for processing reactants therein. WO/2009/023515, CAN 150:216733.2009

(20) The development run is described in terms of g/h, while the scale-up run is described in terms of kg/d. The development run could also be described as 120 g/d.

(21) The data included in Figure 3 were collected when the reaction phases were not split for sampling, compared to Figure 7 which shows a separate data set for each of the incoming phases of the biphasic reaction. Additionally, the product wt % in Figure 3 was elevated due to solvent loss.

(22) Fogler, H. S. *Elements of Chemical Reaction Engineering*, 3rd ed.; Prentice Hall PTR: Upper Saddle River, NJ, 1999.

(23) Relative supersaturation was calculated from $(C - C^*)/C^*$ where C = the steady-state liquid concentration of API and C^* = the equilibrium concentration value.

(24) In all other reaction conditions a tertiary amine was utilized for formation of the acylsulfonamide. As discussed in the previous publication on this work (ref 12), this color was attributed to the reaction of tertiary amines with the acid chloride to generate benzamide that was highly colored.

(25) While all other unit operations were run at 5.2 g/h, the crystallization was run at a 2.1 g/h rate to reserve material for additional crystallization studies. Additionally, this mass is lower due to the large number of samples that were collected from the crystallization reactors to better understand the process.

(26) The success of the large-scale version of the gravity overflow resulted in the design of a small-scale version that has been presented at the Denver ACS: White, T. D.; Berglund, K. D.; Groh, J. M.; Johnson, M. D.; Yates, M. H. Development of a Continuous Schotten−Baumann Route to an Acyl Sulfonamide. *Abstracts of Papers*; 242nd ACS National Meeting and Exposition, Denver, CO, United States, August 28−September 1, 2011.

(27) Atlas pumps were utilized for this addition: http://www.syrris.com/batch-products/atlas-syringe-pump

(28) The tubing that was chosen for evaluation was L/S High-Performance Precision GORE STA-PURE (http://www.masterflex.com) with 1/4 in. ID and 1/16 in. wall thickness due to known compatibility with organic solvents. The compatibility with the extraction solvent system (4:1:2.5 v:v isopropyl acetate/2-MeTHF/toluene) was tested by running the mixture through the tubing for 55 h and performing gravimetric analysis of the blank solvent system compared to the solvent that had recycled through the system. No evidence of leachables was observed, and the tubing showed no evidence of breakdown.

(29) FloPRo sampler utilized to collect samples during the extraction unit operation. See http://www.globalfia.com/.

(30) The correlation of feeds that equate to isolated solids is an approximation because the process was continuous and feeds were not stopped.

(31) The normal feed rate was doubled as the batch startup was run with enough material to fill CSTR 1 and 2.

(32) Both isopropyl acetate/isopropanol add-backs are 3 vol based on the known wt % of product contained in a known charge based on the balances used for the feed can for the distillation.

(33) For two of the lots of material the effect of more frequent, 1 kg washes once every 3 h was investigated, in addition to the 50 g wash used to flush the piping to the filter every 30 min (after every sixth slurry transfer to the filter, the cake was washed with 1 kg of 1.5:1:88.3 isopropyl acetate/isopropanol/heptane), but this provided no advantage over the single wash.