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Compact and Integrated Approach for Advanced End-to-End Production, Purification, and Aqueous Formulation of Lidocaine Hydrochloride

Jean-Christophe M. Monbaliu,[†,‡] Torsten Stelzer,[†,§] Eve Revalor,[†,∥] Nopphon Weeranoppanant,[†] Klavs F. Jensen,[*,†] and Allan S. Myerson[*,†]

[†]Department of Chemical Engineering, Massachusetts Institute of Technology 77 Massachusetts Ave., Cambridge, Massachusetts 02139, United States

[‡]Center for Integrated Technology and Organic Synthesis, Department of Chemistry, University of Liège, B-4000 Liège (Sart Tilman), Belgium

[§]Department of Pharmaceutical Sciences, University of Puerto Rico, Medical Sciences Campus, San Juan, Puerto Rico, United States

[∥]Department of Chemical and Biomolecular Engineering, Melbourne Medical School, University of Melbourne, Melbourne, 3010 Victoria, Australia

Supporting Information

ABSTRACT: A compact, fully integrated, and automated system is developed for end-to-end production, purification, and formulation of the active pharmaceutical ingredient (API) lidocaine hydrochloride, a widely used local anesthetic. The purification strategy includes appropriate combination of extraction, reactive crystallization, and antisolvent cooling crystallization that enables the production of lidocaine hydrochloride formulated solution, for topical application meeting US Pharmacopeia (USP) standards. On the basis of the optimal yield observed in each step, the system sustains a daily production of 810 doses (dosage strength = 20 mg mL^{-1}, i.e., 2% formulation in commercial denomination).

1. INTRODUCTION

The American Chemical Society (ACS) Green Chemistry Institute (GCI) and global pharmaceutical companies established the ACS GCI Pharmaceutical Roundtable to encourage the integration of green chemistry and engineering into the pharmaceutical industry.[1] Innovative small-scale, multipurpose continuous manufacturing[2] appears to be particularly well-poised to contribute to the movement toward green, sustainable processes and was voted as a top research priority.[3,4] Moreover, decentralized, small-scale (table-top), versatile, and flexible pharmaceutical manufacturing platforms (PMP) combining the actual synthesis of the active pharmaceutical ingredients (APIs), with advanced end-to-end purification strategies and final formulation could afford a potential solution against drug shortages.[2] The growing and threatening global problem of drug shortages[5−7] has been thoroughly reviewed by the United States Food and Drug Administration (FDA).[8] This report emphasizes that the majority (72%) of the primary reasons for drug shortages are related to manufacturing and supply chain issues[8] in today's centralized and batch-dominated pharmaceutical industry.[9] Moreover, portable, decentralized, end-to-end PMPs could enable on-demand manufacturing strategies for various medicines as in epidemic or crisis outbreaks.[2]

The realization of PMPs demands various innovations in chemistry, chemical engineering, separation processes, automation, and process control via process analytical technologies (PATs) to achieve high standards of product quality.[2,10−12] Beyond technology and innovation, targeting high standards in product quality requires the integrated design of simple yet effective organic synthesis routes that are controlled at the very upstream ends of the process to limit the formation of impurities in the first place. Such a sustainable approach inherently reduces the complexity of the entire manufacturing process because it simplifies downstream purification and separation steps and hence reduces the environmental footprint of the overall process.[13]

Since its clinical introduction by Astra in 1947, lidocaine hydrochloride is considered as one of the most widely used local aminoamide anesthetics and most essential medications needed in a basic healthcare system. Partially because it is no longer used as a first-line antiarrhythmic, the production of aqueous lidocaine has declined, resulting in its placement on the FDA shortage list.[14] However, lidocaine hydrochloride in aqueous solution remains a highly versatile medication. With very little modification of the final formulation, i.e., addition of one excipient, lidocaine hydrochloride aqueous solution can be used as a topical local anesthetic,[15,16] as a subcutaneously injected local anesthetic,[17−19] or as an intravenous antiarrhythmic used during resuscitative measures.[20,21] Lidocaine hydrochloride is a very attractive API due to this versatility, which precisely fits the purpose of the PMP by producing a concentrate modifiable on demand.

In this contribution, we report on the design of a compact and integrated process for the production, advanced end-to-end

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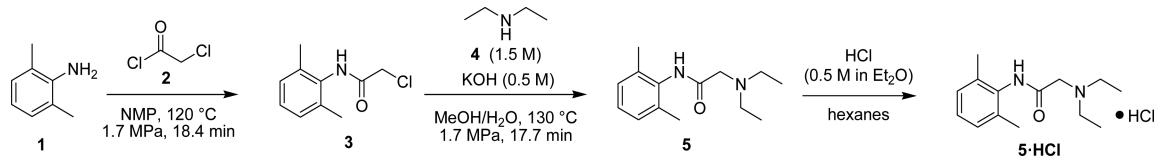
Scheme 1. Preparation of Lidocaine Hydrochloride (5·HCl) from 2,6-Dimethylaniline (1)



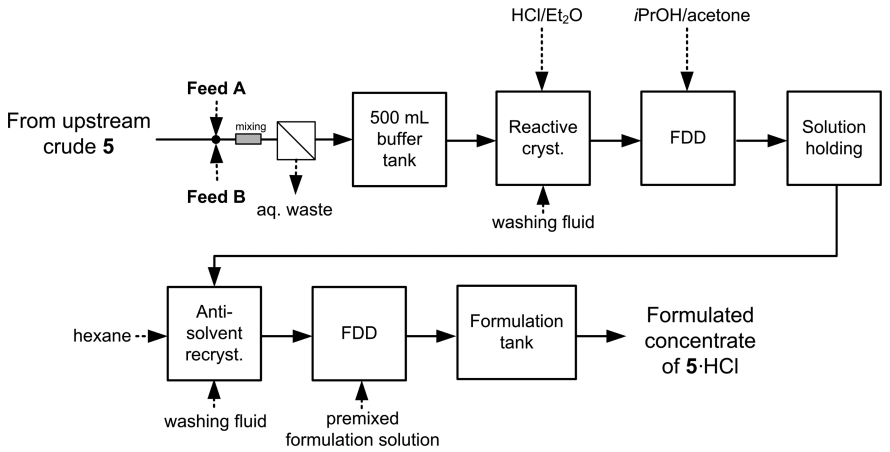


Figure 1. Process flow diagram for end-to-end purification and formulation of lidocaine hydrochloride (5·HCl) including all major unit operations. Upstream extraction of lidocaine free base (5), as well as downstream reactive crystallization, filtration−drying−dissolution (FDD), antisolvent cooling crystallization, and formulation.

purification strategy, and aqueous formulation of lidocaine hydrochloride in a fully automated setup. To achieve this ambitious goal, up- and downstream components are designed by integrated process design approaches,[13,22] in concordance with the PMP requirements. The results emphasize the key process parameters to control the level of impurities in the upstream components to ensure efficient downstream purification and formulation. A combination of appropriate additives and extraction techniques at the junction of the up- and downstream components ensures that downstream processes are not affected by the increase of a particular impurity (diethylamine hydrochloride) generated in upstream unit operations. Diethylamine hydrochloride reduces the efficiency in the downstream purification sequence consisting of reactive and antisolvent crystallization, respectively. This comprehensive approach sustains the production of an aqueous formulation of lidocaine hydrochloride[23] in agreement with US Pharmacopeia (USP) standards.[24]

2. EXPERIMENTAL METHODS

2.1. Materials. 2,6-Dimethylaniline (99%), chloroacetyl chloride (≥99%), diethylamine (≥99%), potassium hydroxide (KOH, ACS reagent, ≥85%), sodium chloride (NaCl, ACS reagent, ≥99%), ammonium chloride (NH_4Cl, ACS reagent, ≥99.5%), 1-methyl-2-pyrrolidone (NMP, ACS reagent, ≥ 99%), methanol (MeOH, ACS reagent, ≥ 99.8%), hexane (mixture of isomers, ACS reagent, ≥98.5%), sodium carboxymethyl cellulose, diethyl ether (HPLC grade, ≥99.9%, inhibitor-free), hydrochloric acid (2 M) in diethyl ether, acetone (ACS reagent, ≥99.5%), and 2-propanol (ACS reagent, ≥ 99.5%) were purchased from Sigma-Aldrich and used as received without further purification. DI water was obtained from a Milli-Q, Millipore system. For reference purposes, a commercial sample of lidocaine hydrochloride was acquired from Shunyi Bio-Chemical Technology Co, Ltd., China and purified upon reception by recrystallization.

2.2. Synthesis (Upstream). Lidocaine hydrochloride (5·HCl) was obtained by reactive crystallization from lidocaine free base (5). 5 was produced via a telescoped two-step process (Scheme 1) from the acylation of 2,6-dimethylaniline (1) with chloroacetyl chloride (2) toward 2-chloro-*N*-(2,6-dimethylphenyl)acetamide (3), which was then reacted with diethylamine (4) in a continuous-flow tubular reactor.[2]

All wetted parts were constructed from high-purity PFA (tubing: 1/16″ I.D., 1/8″ O.D., McMaster-Carr), PEEK (tees: 1/4-28 thread for 1/8″ O.D. tubing, 0.05″ thru hole, Upchurch Scientific; cross junctions: 1/4-28 thread for 1/8″ O.D. tubing, 0.05″ thru hole, Upchurch Scientific; nuts: 1/4-28 thread for 1/8″ O.D. tubing, Upchurch Scientific), ETFE (super flangeless ferrules: 1/8″ O.D. tubing, Upchurch Scientific), and glass. Samples for off-line analysis were treated under process conditions on the bench prior to the analysis. The pumping of chemicals was performed using piston pumps (Smartline 100) from Knauer, Germany and dual syringe pumps (LDP-5) from Labortechnik Heinz Sewald, Germany. The continuous-flow setup (Scheme 1) consisted of two PFA tubular reactors kept under 1.7 MPa generated by using a back-pressure regulator.[25] In the first section of the tubular reactor (10 mL internal volume, 18.4 min residence time), 1 (1.43 M in NMP) was reacted with a slight excess (1.15 equiv) of 2 (4 M in 1-methyl-2-pyrrolidone) at 120 °C. The intermediate 3 was then reacted with 3 equiv of 4 (1.5 M in MeOH) in the presence of 0.5 M aqueous KOH in the second section of the tubular reactor (30 mL internal volume, 17.7 min residence time) to yield 5 (99%> conversion, HPLC).

2.3. Extraction (Upstream). Crude 5 was extracted from the reactor effluent by the concomitant injection of an organic solvent (Feed A: ethyl acetate, toluene, methylisobutyl ketone, diethyl ether or hexane) and water or an aqueous solution

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(Feed B: DI water or aqueous solution of sodium chloride and/or ammonium chloride) (Figure 1) through a PEEK cross-junction. Before transfer to a liquid−liquid separator, the resulting mixture was homogenized via a short packed-bed column (packing: 0.1 mm glass beads).[26] The organic layer was then conveyed to a buffer tank for further processing in the downstream unit utilizing a solenoid diaphragm-metering pump (FMM20) from KNF Neuberger, Germany. Unless otherwise specified, the FMM20 pump type was used for all downstream solvent and solution transportation. Crude **5** in the extraction solvent was collected at a flow rate of 3 mL min^{-1}. Upon collection of 250 mL, the solution was transferred downstream for further purification steps encompassing reactive crystallization and antisolvent cooling crystallization prior to the final formulation. The details of the downstream setup used within this study (Figure 1) are given in the Supporting Information.

2.4. Reactive Crystallization (Downstream). The most common formulation of commercial lidocaine is a hydrochloride salt (**5**·HCl),[23] which was obtained from lidocaine free base (**5**) through reactive crystallization with a diethyl ether solution of hydrochloric acid (0.5 M). The reactive crystallization was conducted at 10 °C in a jacketed HDPE (high-density polyethylene, FDA compliant) reaction tank (400 mL, 9 h residence time) equipped with a PTFE (commercially available from Sigma-Aldrich) coated marine-style impeller stirred at 320 rpm and temperature-controlled using a thermoelectric liquid cooler (LC-035) from TE Technology, Inc., USA (see Figure S1 in the Supporting Information for detailed information regarding the in-house built reaction tank). Once 250 mL of crude **5** solution (0.11 M) was transferred into the reaction tank, the HCl solution (82.5 mL, 0.5 M in diethyl ether) was added at a flow rate of 0.1 mL min^{-1}. The molar ratio of the acid solution to **5** was kept at 1.5:1 to obtain **5**·HCl. The resulting **5**·HCl was filtered, washed (250 mL hexane), and dried (50 °C, vacuum 400 mPa, residence time 60 min) in an in-house constructed filtration−drying−dissolution unit (FDD) equipped with a Hastelloy filtration membrane. After redissolving in a premixed solution of acetone/isopropanol (96:4 wt %) at 50 °C to reach a feed concentration of 34.6 mg mL^{-1}, the solution was transferred to the final purification step of **5**·HCl. Samples for off-line analysis were treated under process conditions on the bench prior to the analysis.

2.5. Antisolvent Cooling Crystallization (Downstream). The final purification of **5**·HCl was performed through an antisolvent (hexane) cooling crystallization process from 50 to 5 °C. **5**·HCl was transferred into a jacketed HDPE crystallization tank (100 mL, 2.5 h residence time) equipped with a PTFE coated marine impeller stirred at 200 rpm and temperature-controlled using a thermoelectric liquid cooler (LC-200) from TE Technology, Inc., USA. For detailed information regarding the in-house built crystallization tank, the reader is referred to the online available Supporting Information. Hexane (40 vol. %) was then added with a flow rate of 2 mL min^{-1} while cooling down from 50 to 5 °C with a cooling rate of 1 K min^{-1} (see Figures S6 and S7 in the Supporting Information for solid−liquid equilibrium data). After the crystallization, the crystals of 5·HCl were filtered, washed (100 mL hexane), and dried (50 °C, vacuum 400 mPa, residence time 120 min) in another in-house built FDD prior to formulation (Figure 1). Samples for off-line analysis were treated under process conditions on the bench prior to the analysis.

2.6. Formulation (Downstream). Upon completion of the drying cycle, 50 mL of a premixed aqueous solution of sodium carboxymethyl cellulose was added to resuspend and dissolve the crystals at a stirring rate of 200 rpm in the FDD. Finally, the solution was drained into the formulation tank, and the real-time concentration was monitored in situ employing an ultrasound analytical system (LiquiSonic 30) from SensoTech GmbH, Germany, equipped with a Hastelloy probe able to measure temperature and ultrasonic velocity utilized to calculate the concentration.[12] For detailed information regarding the in-house built formulation tank the reader is referred to Figure S4 in the online available Supporting Information.

2.7. Methods. *X-ray Powder Diffraction (XRPD).* XRPD was performed at ambient conditions using a PANalytical MPD X'Pert Pro diffractometer with copper as the anode material (Cu Kα radiation 1.541 Å) and X'Celerator high-speed detector in the 2θ scan range from 5° to 40°.

High-Pressure Liquid Chromatography (HPLC). An HPLC method for **5** was developed using an Agilent 1260 Infinity system equipped with Zorbax Eclipse Plus column (C18, 4.6 × 100 mm, 3.5 μm) temperature-controlled at 25 °C and a UV detector (254 nm), with a gradient mobile phase consisting of 10 mM Na_2HPO_4 aqueous solution and 1:1 MeOH/MeCN organic solution at a 1.5 mL min^{-1} total flow rate (characteristic retention time = 9.7 min).

HPLC analysis for **5**·HCl was performed by injecting 20 μL onto an Agilent 1260 Infinity system equipped with Agilent Pursuit 5 C18 column (3.9 × 300 mm) temperature-controlled at 25 °C and an UV detector (254 nm). The mobile phase was pumped at constant flow rate of 1.5 mL min^{-1} and consisted of 1:4 (V/V) mixture of acetonitrile and Solution A (water and glacial acetic acid, 930:50, V/V) adjusted with 1 M aqueous sodium hydroxide to a pH of 3.4.[24] The characteristic retention time of **5**·HCl is 4−6 min.

Nuclear Magnetic Resonance (NMR). ^{1}H NMR spectra were recorded on a Varian Oxford 300 MHz spectrometer in $CDCl_3$ (**5**), d_6-DMSO, or D_2O (**5**·HCl).

3. RESULTS AND DISCUSSION

3.1. Extraction (Upstream). The impact of Feed A (Figure 1) on the extraction of **5** from the crude reactor effluent was investigated. The crude reactor effluent consisted of a tertiary NMP/MeOH/water mixture flowing at 1.65 mL min^{-1} and containing essentially pure **5** and the excess of diethylamine (**4**). Various organic solvents were tested such as ethyl acetate, toluene, methylisobutyl ketone, diethyl ether, or hexane at different flow rates. The injection of Feed A was first tested alone, without the injection of Feed B (DI water or aqueous solutions). Regardless of the amount injected, ethyl acetate, toluene, and methylisobutyl ketone each formed a stable emulsion, with a significant impact on the extraction efficiency, hence giving low yields. In contrast, the injection of diethyl ether or hexane led to rapid phase separation. While hexane led to only 30% recovery for the extraction of **5** after a one-stage extraction, diethyl ether performed extremely well under the same conditions with 60% recovery (HPLC). However, it was noticed that, despite the superior extraction performance, diethyl ether solutions of **5** led to major issues further downstream due to cumbersome purification and isolation of **5**·HCl (see discussion in section 3.2). Hexane was therefore selected as extraction solvent, since it considerably eased the downstream purification of **5**·HCl. The limited solubility of **5** in

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hexane at room temperature (<14 mg $g^{-1}_{Solvent}$, Figure S5 in the Supporting Information) was not regarded as a limiting factor for the first step of downstream purification (reactive crystallization) due to its low upstream concentration (0.11 M).

Direct in-line extraction of **5** from the crude reactor effluent gave poor yield with one volume equivalent of hexane (1 mL min^{-1}), yet affording **5** in very high purity (HPLC) with only traces of NMP. A larger volume of hexane (3 mL min^{-1}) significantly increased the extraction of **5** and performed similarly to one volume equivalent of diethyl ether. Higher temperatures (50 or 70 °C) did not improve the extraction performance, despite a higher solubility of **5** in hot hexane (Figure S5 in the Supporting Information).

To further improve the extraction performance, concomitant injection of A (1−3 mL min^{-1}) and B in the reactor effluent (1 volume equivalent) was explored. DI water increased the extraction of **5** up to 80% (Figure 2). Next, several additives in

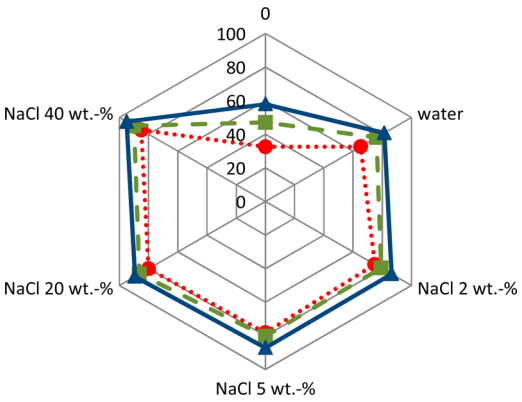

Figure 2. Optimization of the extraction of lidocaine (**5**) from a tertiary NMP/MeOH/water mixture. Extraction performance is given in % (HPLC yield). Various concentrations were studied for the aqueous additive (0, 2, 5, 20, and 40 wt % sodium chloride in DI water, 1 volume equivalent). The red dots, green squares, and blue triangles correspond to the injection of hexane at flow rates of 1, 2, and 3 mL min^{-1}, respectively.

Feed B were considered, and the best results were obtained by salting out **5** with aqueous sodium chloride. The results for the extraction of **5** with the concomitant injection of hexane (1−3 volume equivalent) and aqueous solutions of sodium chloride (1 volume equivalent with different concentrations) are presented in Figure 2.

Optimum extraction of **5** with 95% yield was obtained by combining hexane (3 mL min^{-1}) and saturated aqueous sodium chloride (~40 wt %, 1 volume equivalent). Although satisfying extraction results of **5** with aqueous sodium chloride (Method A) could be achieved, it also forced significant amounts of **4** (up to 40%) to transfer into the organic phase, hence causing purification issues upon reactive crystallization with HCl (see section 3.2). However, the presence of **4** in large excess (3 equiv) was necessary in the upstream process to achieve fast (>20 min) and quantitative conversion of intermediate **3**. Reducing the excess of **4** in the upstream component of the process led to incomplete conversion of **3**, precipitation issues and affected the purity of **5**.

Rather than modifying the entire upstream chemical process toward **5**, an alternative extraction method was assessed (Method B). The combination of an increased ionic character of Feed B with a weak acid within the appropriate pK_a range could indeed enhance the selective extraction of **5** without sacrificing the purity. The best results were obtained using ammonium chloride as an additive to Feed B. With a pK_a of $[NH_4^+/NH_3]$ = 9.2, ammonium chloride enabled the selective extraction of **5** (pK_a $[C_{14}H_{23}N_2O^+/C_{14}H_{22}N_2O]$ = 7.8) in hexane, whereas **4** (pK_a $[Et_2NH_2^+/Et_2NH]$ = 11.02) remained protonated in the aqueous phase. Extraction Method B, consisting in the concomitant injection of Feed A (hexane, 3 volume equivalent) and Feed B (aqueous sodium and ammonium chloride, 20 wt % each, 1 volume equivalent) through a PEEK cross-junction, afforded **5** with 90% yield (HPLC) and, more importantly, free of **4**.

Next, Methods A and B were compared within the downstream operations toward the formulation of **5**·HCl. From each method, 250 mL of crude **5** in hexane (0.11 M) was separately collected in a buffer tank, and then transferred downstream for further purification.

3.2. Reactive Crystallization (Downstream). The solution of crude **5** (0.11 M in hexane, 250 mL) was transferred from the buffer tank into the reaction tank (10 °C) and treated under stirring with 82.5 mL of a 0.5 M solution of hydrochloric acid in diethyl ether with a molar ratio of hydrochloric acid to **5** of 1.5:1. An excess of hydrochloric acid was required to ensure optimal conversion of **5** to **5**·HCl within a reasonable time frame (see Figures S18 and S19 in Supporting Information). The addition flow rate for the hydrochloric acid solution was considered critical and kept at 0.1 mL min^{-1}. Faster flow rates caused the precipitation of an amorphous and gum-like **5**·HCl leading to massive incrustations on the impeller, shaft, and reactor walls (see Supporting Information). Moreover, even if crystallinity is not as important as purity and yield since **5**·HCl was redissolved for further downstream processing, a slower addition rate drastically increased the crystallinity of **5**·HCl (Figure 3).

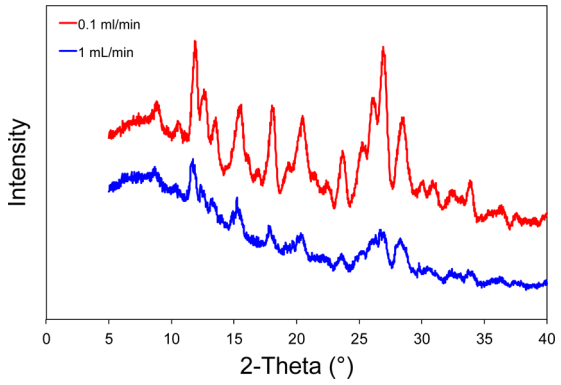

Figure 3. X-ray diffraction patterns for lidocaine hydrochloride (**5**·HCl) obtained by the addition of HCl (0.5 M in diethyl ether) at flow rates of 1 mL min^{-1} (blue) and 0.1 mL min^{-1} (red).

The X-ray diffraction patterns in Figure 3 clearly emphasize that the crystals obtained with slow HCl feed rate have a much stronger baseline with sharper and narrower peaks. Faster feed addition rates led to higher supersaturation levels in the reaction tank, resulting in the formation of a sticky gum-like material. Slow addition of the HCl solution is thus critical to keep both nucleation rate and crystal growth rate at a suitable level to ensure high crystallinity. When diethyl ether was used as the extraction solvent for **5** (see section 3.1), **5**·HCl crashed

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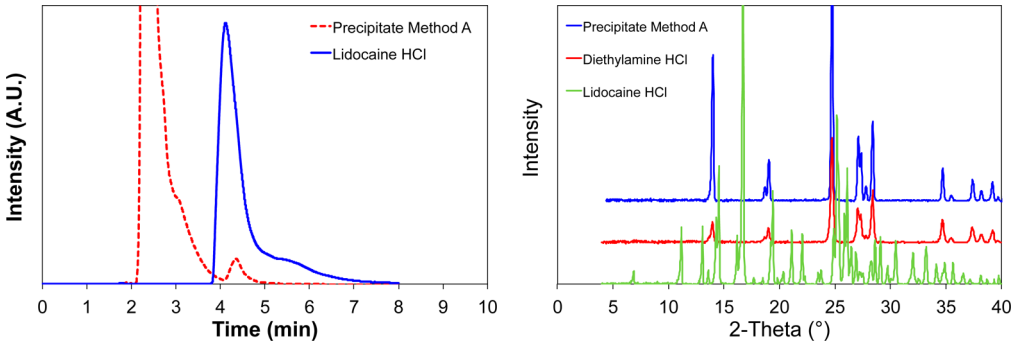

Figure 4. Left: HPLC chromatograms of lidocaine hydrochloride (**5**·HCl), reference sample (blue solid line) and of the solid precipitate obtained after reactive crystallization on a sample collected applying extraction Method A (red dashed line). Right: X-ray diffraction patterns of (bottom to top): lidocaine hydrochloride (**5**·HCl, reference sample, green), diethylamine hydrochloride (**4**·HCl, reference sample, red), and the solid precipitate obtained after reactive crystallization on a sample collected applying extraction Method A (blue).

out as a sticky amorphous material, even at very low addition rates of HCl, therefore precluding further handling.

Although **5** is sparingly soluble in hexane, **5**·HCl is virtually insoluble in the resulting hexane diethyl ether mixture and spontaneously precipitated under the optimized conditions. A prolonged holding time of 8 h supported the formation of a suspension of finely divided crystals of **5**·HCl, that prevented incrustation of the impeller, shaft, reactor wall, and transfer line (see Figure S24 in the Supporting Information) as well as clogging of the sintered porous Hastelloy plate (media grade 0.5) in the subsequent FDD for solid/liquid separation.

In order to compare the effect of the upstream extraction method on the downstream purification, solutions of **5** obtained from extraction Methods A and B (see section 3.1) were both submitted to the optimized reactive crystallization conditions to produce **5**·HCl. Reactive crystallization of the solution obtained from Method A, containing significant amounts of **4**, led to a concomitant crystallization of **4**·HCl and **5**·HCl in a maximum ratio of 39:61 (^{1}H NMR ratio). Moreover, the more basic **4** appeared to react faster with HCl in a first stage, leading to a selective reactive crystallization to some extent: after 30 min ripening, pure **4**·HCl crystallized, while after prolonged ripening, **5**·HCl started to cocrystallize and formed 75:25 and 39:61 **4**·HCl/**5**·HCl mixtures (^{1}H NMR ratio) after 2 and 13 h, respectively (see Figures S11−14 in the Supporting Information). The HPLC data in Figure 4 illustrates that the reactive crystallization of a solution of crude **5** produced upstream by applying Method A led to crystalline material containing mostly **4**·HCl with a small amount of **5**·HCl (30%, HPLC yield). Under these conditions, most of free base **5** remained in solution in the mother liquor.

In addition to low yield and selectivity, extraction Method A ultimately led to severe corrosion issues in the downstream units, most likely due to the presence of large amounts of **4**·HCl. Unlike the reaction tank that was machined out of HDPE to sustain acidic conditions, the crystallization tank was machined out of 316L stainless steel for better heat transfer during the antisolvent cooling crystallization process (see below) and showed evidence of severe corrosion after the recrystallization process on **4**·HCl/**5**·HCl mixtures.

Contrastingly, reactive crystallization on the solution obtained from Method B led to a crystalline material containing exclusively **5**·HCl, with no detectable traces of **4**·HCl (^{1}H NMR, HPLC). In addition to significantly higher yield and purity (95% and 94%, respectively), no corrosion issues were noticed while using Method B.

3.3. Antisolvent Cooling Crystallization (Downstream). Crude **5**·HCl obtained after reactive crystallization (extraction method B) was next purified by an antisolvent cooling crystallization step prior to its formulation. On this account, a one-step antisolvent cooling crystallization was applied to meet USP specification for **5**·HCl (purity 97.7%, HPLC).[24] Initial screening studies of the nucleation kinetic of **5**·HCl emphasized a wide metastable zone in the selected acetone/isopropanol solvent mixture (96:4 wt %), which required a high initial concentration of **5**·HCl (400 mg mL^{-1}) for a cooling crystallization within a reasonable residence time (Figure 5). Given the low concentration of **5**

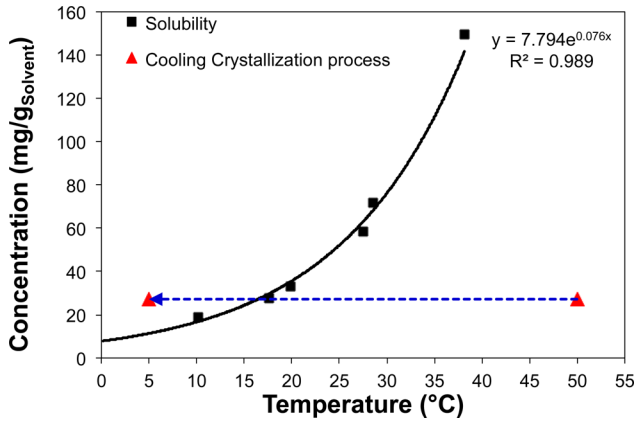

Figure 5. Solid−liquid equilibrium (black squares) of **5**·HCl (Sigma-Aldrich) in a 96:4 acetone/isopropanol mixture. Red triangles refer to the initial and final temperatures for a cooling crystallization process for **5**·HCl with a feed concentration of 34.6 mg mL^{-1}.

in the solution conveyed from the upstream (0.11 M) and the low **5**·HCl feed concentration (34.6 mg mL^{-1}) in the final recrystallization process, the above-mentioned requirement regarding residence time could not be met. Consequently, prepurification experiments with evaporative crystallization were conducted to generate supersaturation by slow evaporation of the solvent, a more suitable crystallization technique for the given flat solid−liquid equilibrium (SLE) characteristic of **5**·HCl at low feed concentrations (Figure 5). However, these studies (data not shown) led to extensive incrustation on the wall of crystallization tank and thus very low yield.

Due to the unsuccessful attempts of cooling and evaporation crystallization of crude **5**·HCl, an antisolvent cooling

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crystallization process was developed (see Figures S6 and S7 in the Supporting Information for SLE data). Antisolvent cooling crystallization is the most efficient way of generating supersaturation to induce nucleation within a reasonable time frame while minimizing incrustation issues in PMPs.[2] For **5**·HCl, it was achieved by adding hexane at a flow rate of 2 mL min^{-1} to a 34.6 mg mL^{-1} feed solution of **5**·HCl in acetone/isopropanol (96:4 wt %) under moderate stirring (200 rpm) to enable the rapid incorporation of the antisolvent into the solution resulting in spatially uniform supersaturation levels[27] while cooling from 50 to 5 °C. The crystals of **5**·HCl were filtered, washed, and dried under vacuum in a FDD prior to formulation. Ultimately, this revised crystallization process afforded crystals of **5**·HCl (88% yield, 97.7% HPLC purity), meeting USP standards[24] within a reasonable time frame and without major incrustation issues.

3.4. Formulation. For the aqueous formulation of **5**·HCl, the crystals were dissolved in a premixed aqueous solution of sodium carboxymethyl cellulose to yield a final concentrate of 34.3 mg mL^{-1}. The concentration was monitored in situ using a ultrasound system capable of monitoring both temperature and ultrasound velocity,[2,28] and was afterward confirmed by off-line HPLC measurements. Overall, this PMP sustained the production of 810 doses per day of formulated **5**·HCl (dosage strength = 20 mg mL^{-1}, Figure 6)[23] based on the optimal yield observed in each step of the integrated end-to-end purification strategy developed (Figure 1).

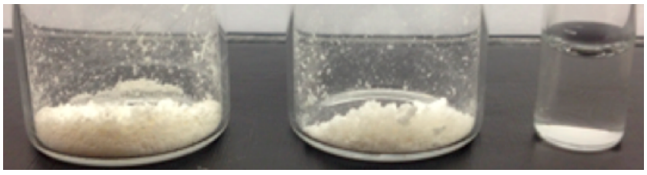

Figure 6. From left to right: photographs of lidocaine hydrochloride (**5**·HCl) obtained after reactive crystallization (purity 94%, HPLC); **5**·HCl obtained after antisolvent cooling crystallization (purity 97.7%, HPLC), and formulated **5**·HCl (20 mg mL^{-1}).

4. CONCLUSION

This study illustrates an integrated approach for the design of a novel pharmaceutical manufacturing platform (PMP) for the production, purification, and formulation of lidocaine hydrochloride. The PMP encompasses advanced end-to-end purification strategies, innovative solutions for extraction, reactive crystallization, antisolvent cooling crystallization, and aqueous liquid formulation of lidocaine hydrochloride. The integration of an efficient extraction strategy at the end of the upstream section of the process, with the subsequent removal of a particular impurity (diethylamine hydrochloride), enabled the implementation of a simplified and efficient downstream purification process with a reduced footprint. This PMP sustains a daily production of 810 doses with a 2% formulation. PMP could afford an efficient and sustainable pharmaceutical manufacturing strategy to challenge drug shortages.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.oprd.6b00165.

Details regarding the unit operations, determination of solute-liquid equilibrium, characterization of the chemical intermediates and final product by Nuclear Magnetic Resonance Spectroscopy, high-pressure liquid chromatography, ultrasound monitoring, determination of molar ratio, and additional experimental information (PDF)

■ AUTHOR INFORMATION

Corresponding Authors

*E-mail: kfjensen@mit.edu (K.F.J.).
*E-mail: myerson@mit.edu (A.S.M.).

Author Contributions

J.-C.M.M., T.S., and E.R. contributed equally to this work.

Notes

The authors declare no competing financial interest.

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