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Redesign of a Grignard-Based API Batch Synthesis to a Flow Process for the Preparation of Melitracen HCl

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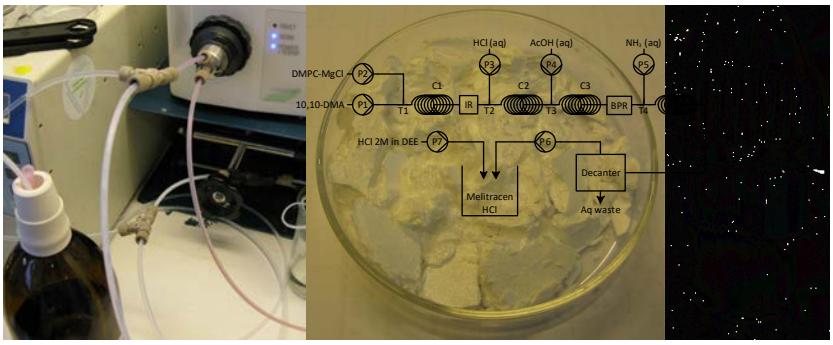
Synopsis


HCl (aq)
AcOH (aq)
NH₄ (aq)
DMPC-MgCl
10,10-DMA
P1
P2
P3
P4
P5
C1
C2
C3
IR
BPR
T1
T2
T3
T4
HCl 2M in DEE
P7
P6
Decanter
Melitracen HCl
Aq waste

Abstract

A Grignard-based batch process, for the preparation of Melitracen HCl, has been redesigned to fit a continuous reactor system. The Grignard addition is carried out at room temperature, with subsequent hydrolysis of the magnesium alkoxide intermediate followed by dehydration of the resulting alcohol. The product is further worked-up by simple gravimetric phase separation and then crystallized with 2 M HCl in diethyl ether to afford pure Melitracen HCl. All steps in the laboratory setup were concatenated and the setup was proven capable of producing a significant portion of the commercial quantities of Melitracen HCl. The flow setup profits from a reduced footprint, lower energy consumption, fewer synthetic steps and reduced raw material usage compared to the batch process.

Keywords: Grignard alkylation, Flow chemistry, API synthesis, liquid phase separation.

Introduction

The efficiency of the pharmaceutical industry has been a widely discussed topic throughout the past decade. The debate has been broad, ranging from early target drug development to the actual production and distribution of pharmaceuticals.[1–6] Expiring patents and empty pipelines have forced pharmaceutical companies to look for alternative methods to remain competitive against generic manufacturers.[7–9] Furthermore, the industry has one of the highest solvent-to-carbon ratios,[10] which in combination with the fact that most of these solvents have high environmental impacts has given the industry a somewhat damaged reputation.[5,10–13] In addition, the authorities have steadily increased the tightening of legislative requirements for pharmaceutical manufacturing, in both development and production.[3,5]

With respect to the production of active pharmaceutical ingredients (APIs), the focus has especially been on batch methods and their insufficiency, especially their mass and heat transfer properties.[14,15] As early as the 1970s, Popov[16] suggested continuous manufacturing as a method for improving the efficiency of pharmaceutical production. However, it was not until the last decade that progress was seen. The establishment of the pharmaceutical round table and the increased interest from academia and industry have been driving the transformation forwards.[4,5,17–20] The authorities have since 2002 acknowledged new production methods and strategies within manufacturing. Process analytical technology (PAT) approaches and Quality-by-Design (QbD) concepts have been important factors in the acceptance of continuous manufacturing by the authorities.[9,21,22]

Earlier publications concerning the new paradigm of pharmaceutical manufacturing often focused on single synthesis steps and unit operations, often with the use of microreactor technology.[23,24] Later trends have changed the focus towards multiple synthesis steps,

pharmacy-on-demand and end-to-end manufacturing.[17–19,25] As the trend has moved from single step to end-to-end manufacturing,[18] the previous out-scaling concept[23] of microreactors has also been replaced by mini-scale flow systems.[18,20,26–28] The scale-up of a continuous setup needed to meet full-scale requirements is often minor; hence the benefits such as mass and heat transfer are almost comparable to microreactor technology.[15]

Reactions having multiple phases still pose a significant challenge within flow chemistry.[29–31] Flow reactors are known for being poor at handling solid material due to clogging issues, with some exceptions such as packed bed reactors with fixed catalytic material. Breakthroughs for flow reactors that can handle solid reactants or products have within recent years been demonstrated, such as the desulfurization of substituted thioimidazoles by Baxendal *et al.*[32], the powder dosing unit for a CSTR demonstrated by Hu *et al.*[33] and precipitation in flow demonstrated by Baxendal *et al.*[34]

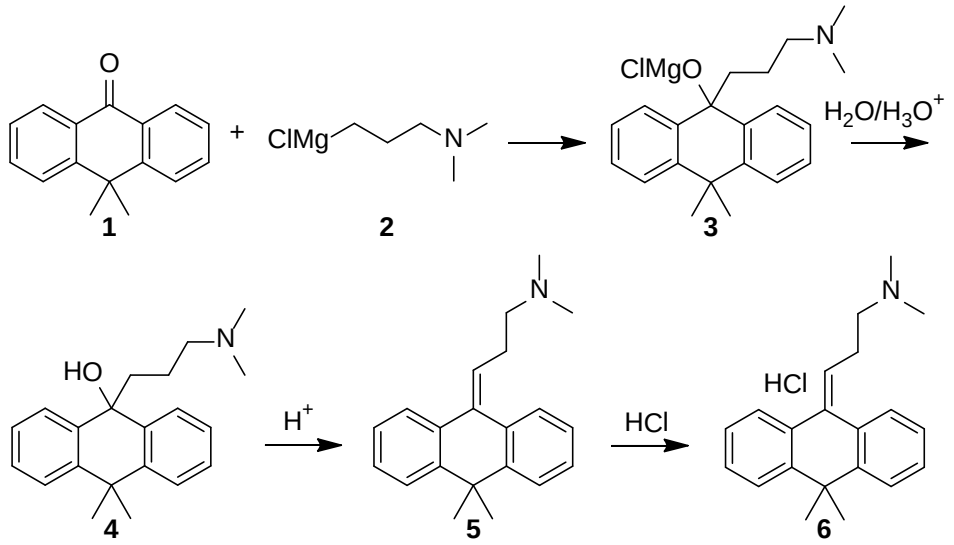
The pharmaceutical industry is notorious for their usage of solid compounds, either as reactants, intermediates or APIs.[29,31] Low solubility is often a huge obstacle for applying the chemistry to a flow setup, unless alternative methods are applied.[2,31] Solubility is one of the key parameters when designing a reactor setup and an instructive discussion may be found in Pedersen *et al.*[20] In cases of high solubility, the simple use of a plug flow reactor (PFR) can be applied, often with great success and larger throughput.[28,35] The challenging part then becomes the purification of the product from impurities and unreacted reactants, as well as the final isolation of the product. Many old batch processes utilize the benefits of precipitation as a purification step, hence altering an old batch process to fit a flow setup requires new ways to overcome these challenges.[2,20,29]

Grignard reactions serve as a commonly used method for the formation of carbon-carbon bonds in the development of APIs[36,37]. The exothermic behavior of the Grignard reaction makes it ideal for continuous production. Several demonstrations of Grignard reactions in flow have been done within the last decade: Kopach *et al.*[38,39] demonstrated the use of a CSTR technology; Pedersen *et. al*[20,26,40] demonstrated the use of a heterogeneous slurry filter reactor; Mateos *et al.*[41] studied the formation of ketone by nucleophilic Grignard addition to nitril groups by use of flow methods; Lonza[42–44] has demonstrated the use of micro reactor technology.

Chemistry

As illustrated in Scheme 1, four synthetic steps are involved in the manufacturing of Melitracen HCl (**6**). The four steps are a classic Grignard addition to a ketone, a hydrolysis of a magnesium alkoxide, a dehydration of an alcohol and a salt precipitation to isolate the API. The Grignard addition is between 10,10-dimethylanthrone (10,10-DMA (**1**)) and 3-(*N*,*N*-dimethylamino)propylmagnesium chloride (DMPC-MgCl (**2**)), resulting in formation of the magnesium alkoxide **3**. The magnesium alkoxide **3** is then hydrolyzed to the alcohol **4** and dehydrated to form product **5**. The last step is a crystallization of the API as a salt, where HCl is added to obtain the Melitracen HCl (**6**).

Scheme 1: Syntheses of magnesium alkoxide **3**, alcohol **4** and dehydrated product **5** in the manufacturing process of Melitracen HCl **6**, from ketone **1** and Grignard reagent **2**.



87

88 **Current Batch Synthesis**

89 The current batch synthesis involves individual synthetic steps, as illustrated in Figure 1.
90 DMPC-MgCl **2** is made in-house before it is used, due to its limited storage shelf life, in a
91 toluene-THF solvent mixture. THF is present in trace amounts in order to stabilize the
92 magnesium in the Grignard reagents.[45] A solution of 10,10-DMA **1** is prepared in toluene and is
93 slowly transferred to the DMPC-MgCl **2,** maintaining a temperature of 50°C. DMPC-MgCl **2** is
94 used in an equivalence of 1.6 compared to 10,10-DMA **1**. The formed magnesium alkoxide **3** is
95 hydrolyzed with water and acetic acid (80%). The aqueous phase is discarded and concentrated
96 hydrochloric acid (37%) is used to dehydrate alcohol **4** to form dehydrated product **5**. Toluene is
97 replaced with ethanol by a solvent swap. Crystallization of the dehydrated product **5** from the
98 ethanol phase is done with HCl gas to obtain the final Melitracen HCl (**6**), which is subsequently
99 isolated by filtration.

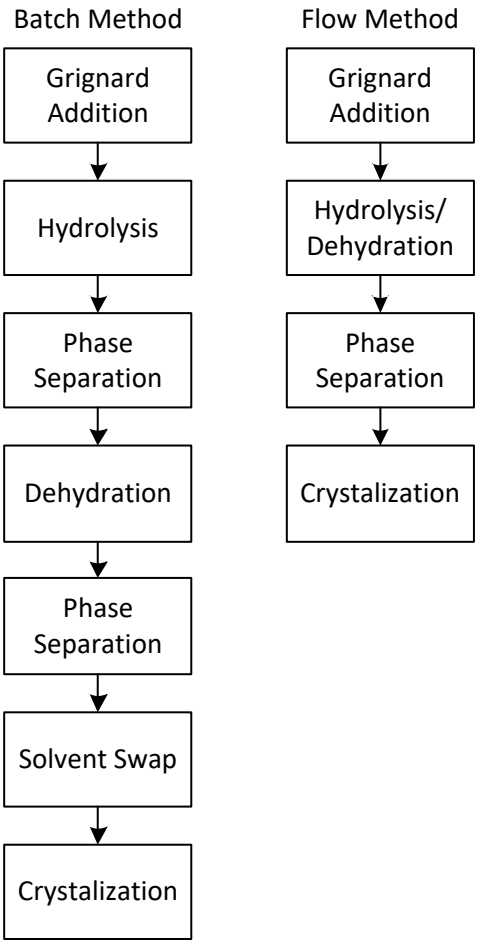


Figure 1: The operational steps involved in the current batch method and the simplification achieved by the flow setup.

Investigational Strategy

The API manufacturing strategy at H. Lundbeck A/S is focused on continuous production. Melitracen HCl synthesis currently occupies significant production facilities and is produced by routine batch synthesis procedures. The process shows potential for being redesigned to fit a continuous reactor setup, with potential for significant simplification of the operation and the synthetic route. This article describes the laboratory work for redesigning the process to fit a continuous reactor setup for the Grignard addition to the final Melitracen HCl crystallization.

Experimental Section

Screening Experiments

The routine batch synthesis for production of Melitracen HCl **6** was considered suitable for redesign into a flow process, as most of the synthetic steps are categorized as fast reactions.[31] The current batch methods could possibly be transferred directly into a flow setup, providing the common benefits achieved when changing from batch to continuous processing. However, additional savings could potentially be achieved with the flow setup if simplifications of aspects such as the solvent choice and synthetic steps were possible. Classic batch screening experiments were conducted to assist in the decision on and design of a flow setup and, based on these experiments, the flow setup decided on was to be experimentally verified afterwards.

Solubility of Reactants and Products in Solvents

The first consideration in the process for redesigning Melitracen HCl **6** synthesis is the solubility of reactants, intermediates and products. Solubility is one of the key parameters when designing a reactor setup. The primary focus was on the Grignard addition step, where reactants 10,10-DMA **1**, DMPC-MgCl **2** and magnesium alkoxide product **3** are of interest. DMPC-MgCl **2** already has a high solubility and was not tested further. 10,10-DMA **1** is a solid starting material and needs to be dissolved before it can react with DMPC-MgCl **2**. The solubility of 10,10-DMA **1** should therefore be tested in potential solvents and at different temperatures. Magnesium alkoxide **3** is not easily isolated, as the magnesium halide part easily reacts with water and moisture. Instead of determining the exact solubility of magnesium alkoxide **3**, a qualitative first estimate of its capability to stay in solution could be sufficient. The requirement is, of course, that the concentration of magnesium alkoxide **3** in the reaction mixture is

representative of the concentrations of the 10,10-DMA **1** and DMPC-MgCl **2** intended for the synthesis. The later synthetic steps should be tested accordingly for solubility where necessary, since low solubility in these steps could require a lower concentration of 10,10-DMA **1** and DMP-MgCl **2** to have a fully operational flow setup from start to end of the synthesis.

The solubility experiments on 10,10-DMA **1** focused on three solvents to be verified: toluene, tetrahydrofuran (THF) and 2-methyltetrahydrofuran (MeTHF), all of which are suitable candidates for later full-scale production. The solubility temperature was tested up to 20°C, which is to be considered the high limit due to ambient temperatures if no heat tracing should be applied to pumps and pipes. Figure 2 shows the solubility of 10,10-DMA **1** in the three solvents, where THF shows a significantly higher solubility than toluene or MeTHF.

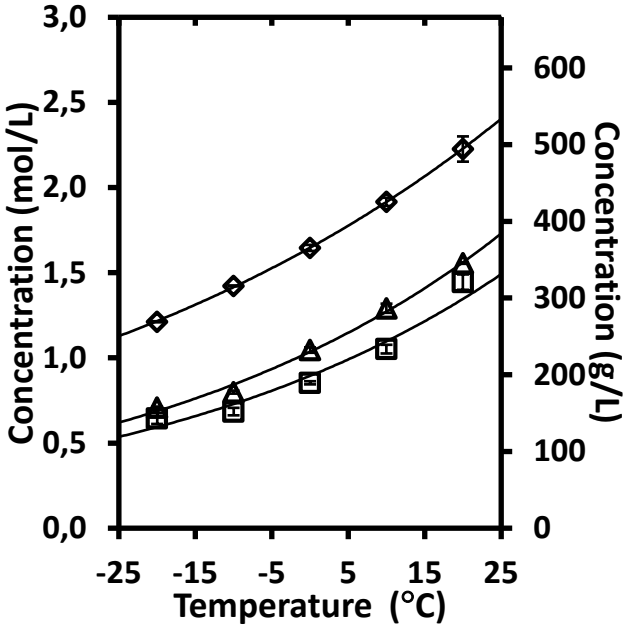


Figure 2: The solubility of 10,10-DMA **1** in toluene (□), THF (◇) and MeTHF (△). The 10,10-DMA **1** has high solubility even at low temperatures in the tested solvents. The solubility in THF is significantly higher compared to MeTHF and Toluene (approximately 100 g/L more 10,10-DMA **1**).

The significantly higher solubility of 10,10-DMA **1** in THF makes it obvious to use THF. If toluene were to be used as in the batch process, trace amounts of ether would still be needed to stabilize the magnesium in DMPC-MgCl **2**.

The concentration of 10,10-DMA **1** in THF was set to the lower side of 20°C (1.8 mol/L, 400 g/L) to minimize the risk of precipitation while operating a flow setup. The DMPC-MgCl **2** was available at approximately 1.5 M concentration in THF from the production and it was decided to proceed with this concentration. A couple of quick qualitative batch experiments were carried out to verify whether the magnesium alkoxide **3** could remain soluble in the reaction mixture, as it was not possible to isolate the unstable magnesium alkoxide **3** for a solubility study. These experiments came out positive for the desired concentrations of 10,10-DMA **1** and DMPC-MgCl **2** and no further testing of the solubility of magnesium alkoxide **3** was found necessary.

Phase Separation: Organic Phase and Aqueous Waste

A batch experiment, representing the expected concentration for the flow setup, was used to verify the potential for phase separation of THF from the aqueous phase. The DMPC-MgCl **2** was slowly added in excess amounts with a dripping funnel to a round-bottom flask of the 10,10-DMA **1** solution. The mixture was afterwards hydrolyzed with water and acetic acid (80%). The addition of the acid caused the pH of the mixture to become slightly acidic (pH ~6) and an one-phase mixture was achieved. The pH was adjusted with aqueous ammonia (25%) and at pH 8 a two-phase mixture appeared. Alcohol **4** was distributed with 63% in the organic phase and 37% in the aqueous, according to HPLC assay. Adjusting the pH in the aqueous phase to 10 with additional aqueous ammonia (25%) resulted in an additional organic phase, with less than 1% alcohol **4** left in the aqueous phase.

Alcohol **4** in the organic phase was then dehydrated with hydrochloric acid (37%), followed by adjustment of the pH to 10 with aqueous ammonia (25%). Adjusting the pH to 10 allowed a phase separation with more than 99% of the product in the organic phase and with a ~99% purity of the dehydrated product **5**. During the hydrolysis and dehydration, a minor precipitation of solid material was formed that easily dissolved as the reaction progressed and should therefore not be a major concern for a flow setup.

At pH ≥ 10 the tertiary amine is completely deprotonated, causing the products **4** and **5** to become almost insoluble in water, thereby achieving excellent separation. At pH ≤ 10 the tertiary amine becomes protonated and is soluble both in the aqueous and organic phase. If a clean phase separation had not been possible, changing the synthesis solvent to MeTHF could have simplified the workup of the products **4** or **5** from the aqueous phase, as MeTHF is not miscible with water.

One-Step Hydrolysis and Dehydration

The ability to phase separate both the alcohol **4** and the dehydrated product **5** in THF enabled a simplification of the targeted flow method. Ideally, hydrolysis and dehydration should be possible in one step, hence saving a phase separation and combining two synthetic steps into one. Screening for a potential acid for the one-step hydrolysis and dehydration was done, focusing on acetic acid and hydrochloric acid, either separately or in combination. Table 1 shows the results of the product formation based on the different acid systems.

Table 1: Screening of different acids for direct hydrolysis and dehydration of the magnesium alkoxide **3** to the dehydrated product **5**.

Acid Solution	Product (%)	Phase Separation (%)
HCl 37% (aq.)	Dehydrated **5** (100%)	>99

AcOH 80% (aq.)	Alcohol **4** (100%)	>99
HCl 37% (aq.)/AcOH 80% (aq.) (1:1)	Dehydrated **5** (90%) Alcohol **4** (10%)	>99

As seen in Table 1, only hydrochloric acid was able to hydrolyze and dehydrate the magnesium alkoxide mixture in one step. The experiment with hydrochloric acid resulted in significant heat development and an immediate precipitation of solids that potentially could be critical, even though it dissolved within a few minutes. An additional set of screening experiments was done to verify the potential of a lower concentration of hydrochloric acid. These experiments were carried out to verify whether the immediate precipitation of solid could be avoided and whether the energy released from the hydrolysis and dehydration could be distributed, as both steps are exothermic. Equal volumes of hydrochloric acid with different concentrations (1, 3, 6, 9 and 12 M) were used. For the concentrations lower than 6 M, it was not possible to achieve full dehydration at ambient temperature. For the concentrations equal to 6 M and higher, full dehydration was obtained, but all concentrations resulted in precipitation of a white solid that dissolved after few minutes of standing. From a production and environmental perspective, the more concentrated hydrochloric acid is the optimal choice; less aqueous waste is generated if the acid used is stoichiometric. Given the fact that precipitation could not be avoided and the production perspective, it was decided to proceed with 12 M hydrochloric acid.

Precipitation of Melitracen HCl from THF

The dehydrated product **5** was crystallized as the final HCl salt in the THF in a batch experiment, in order to remove a solvent swap to ethanol. The crystallization was carried out with 2 M HCl in Et_2O, as this was considered more suited for a later flow process and more easily implemented in the laboratory setup. An equivalence of 1.1 HCl was used and the

requirement was an achievement of pH<2. The mixture was kept stirred during the crystallization and carried out at ambient temperature. After 10 minutes, fine white solids started to form, followed by a massive precipitation of Melitracen HCl **6**. The Melitracen HCl **6** was filtered with a Büchner funnel and washed with THF. The isolated yield was 80% and within the specifications for the in-house analysis methods used in the routine production (CHN, TGA, UV-vis, HPLC, melting point). Figure 3 is a microscope picture of the isolated Melitracen HCl **6**. For full-scale production, the HCl gas would still be more desirable for the crystallization and the 2 M HCl in Et_2O merely serves as a proof of concept for the laboratory flow setup.

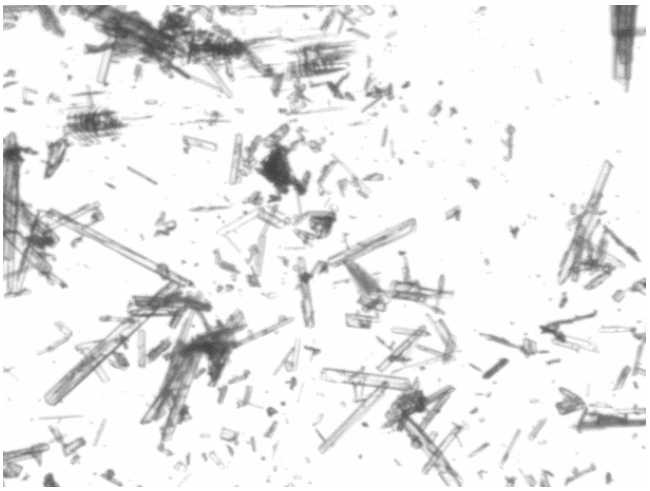


Figure 3: Microscope picture of the isolated Melitracen HCl 6 from the THF solution.

Flow Process

The initial batch screening experiments all indicated that the chemistry should be run in PFRs. This decision is based on several parameters from the screening experiments. In particular, the high solubility of the reactants and products makes the synthesis ideal for PFRs. Additionally, all of the synthesis steps are categorized as fast (full conversion within minutes) and hence small reactor volumes can be used. The final setup is illustrated in Figure 4 as a flow sheet. All tubing was 1/8” OD and 1/16” ID and made from PTFE; the T-mixer was of PEEK material ID 0.04”.

All synthetic steps were performed at ambient temperature, with no active cooling or heating. If the reactor system was to be scaled significantly, consideration of active cooling and heating should be taken into account due to potential safety and control related issues. Every step, except for the addition of acetic acid and the decanter phase separation, is exothermic. The decanter was a 100 mL glass bottle, fitted for the purpose with an in-house-made PTFE lid. After the Grignard addition (T1,C1) of DMPC-MgCl **2** to 10,10-DMA **1**, a flow IR 10 µL head from Mettler Toledo was applied for in-line monitoring of the conversion and reaction. After the acetic acid addition (T3,C3), a 100 psi back pressure regulator (BPR) was applied to avoid boiling of the THF due to the hydrolysis and dehydration taking place at the HCl addition (T2,C2). The choice of placing the BPR is due to precipitation of solid material right after the HCl addition that is fully dissolved throughout the acetic acid coil. The HCl precipitation was done by collection of the two streams in a flask. A number of different pumps were used, all of them being positive displacement pumps for dosing purposes. Knauer Azura P 2.1S HPLC pumps with 10 mL stainless steel pump heads (P1 and P2) were used for the 10,10-DMA (**1**) and DMPC-MgCl (**2**); a Syrris Asia pump (dual pump) equipped with 0.5 and 1.0 mL glass syringes was used for both hydrochloric acid (P3) and acetic acid (P4). A Merck-Hitachi HPLC pump with a 10 mL stainless steel pumphead was used for the aqueous ammonia (P5) and Ismatec Reglo RH00 piston pumps were used for the decanter outlet (P6) and the 2 M HCl in Et_2O (P7). The two Knauer pumps were specially ordered with PTFE gasket intended for Grignard reagents and THF solvent. The remaining pumps were chosen based on availability in the laboratory. The flow rate was determined in accordance with the maximum capacity of each pump and the limitation was the pump used for the acetic acid.

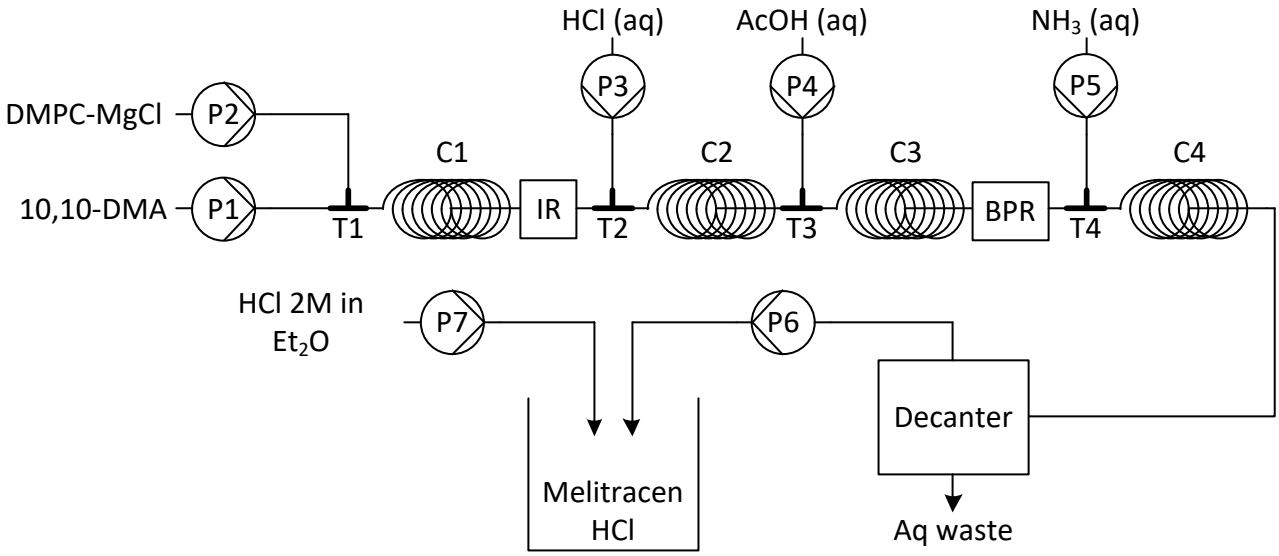


Figure 4: Flow sheet of the flow reactor setup for the redesign of the Melitracen HCl synthesis. Pump (P), Coil (C), T-mixer (T), Infrared In-line flow cell (IR), Back pressure regulator (BPR).

Results and Discussion

Stepwise Verification of Flow Reactor Parts

A stepwise implementation and verification of each step was done to minimize the risk of operational problems, while operating the entire setup as illustrated in Figure 4. The major risks were considered to be clogging issues and separation performance.

The Grignard addition of DMPC-MgCl **2** to 10,10-DMA **1** was the first part to be verified and an equivalence of 1.1 DMPC-MgCl **2** was used to ensure full conversion of 10,10-DMA **1**. Only a few minutes of residence time were needed for the reaction to achieve full conversion of the 10,10-DMA **1**. The reaction was easily followed visually, as the magnesium alkoxide **3** becomes dark red/orange. The product stream was collected in a flask, where it turned to a more orange-like appearance over time.

Implementation of the HCl stream for hydrolysis and dehydration caused boiling of the THF solvent, but full conversion was achieved within minutes. Implementing the acetic acid stream resulted in some alteration of the setup to account for the boiling of the THF, as full conversion was not achieved. A back pressure regulator (BPR) of 100 psi was added to prevent the boiling of the THF (65 °C at STP). The BPR provided a stable flow that ensured a steady residence time in the HCl coil (C2), resulting in the desired full conversion of the magnesium alkoxide **3** to the dehydrated product **5**. Adding the aqueous ammonia stream to the setup caused precipitation of ammonium chloride salt. The precipitate was easily dissolved by addition of water. Due to lack of pumps, it was decided to dilute the acetic acid to 40% from the original 80% and to double the flow rate. From a production perspective, an additional pump with water would be better suited as 80% acetic acid is the standard concentration in production. Acetic acid serves to assure that the magnesium salt complex remains soluble after pH adjustment to basic conditions. The BPR was originally implemented right after the HCl coil, but the white solid precipitate later caused clogging of the BPR, so it was moved to be after the acetic acid stream where a full liquid homogeneous phase was present. The choice of not moving it to be after the aqueous ammonia coil was due to a small risk of having precipitation upon the addition thereof, as this was observed in a previous run. At the end of the acetic acid addition during all adjustments, a full one-phase homogeneous stream was constantly present and it was considered more stable to add the BPR at this point in case of any fluctuation.

Having the entire setup running, the decanter was tested for the setup. A previous flow setup had proved the decanter's capability for separating organic and aqueous phases from each other, so that a single experiment was enough to demonstrate the decanter for this separation. The last stream to be implemented was the 2 M HCl (Et_2O) stream for crystallization. At first, mixing of

the two streams was attempted in a T-mixer (2.5 mm ID), but the low pressure pumps used (Ismatec pumps) could not deliver a high enough pressure to avoid clogging. The clogging was caused by evaporation of the solvents due to the low boiling points of both THF and Et_2O and the crystallization of Melitracen HCl (**6**) happening in the T-mixer. As an alternative, the two streams (P6 and P7) were pumped individually into the collecting bottle. No optimization was done to control the crystallization, as this was not the scope of the project, and for a full-scale setup HCl gas would be a preferred choice. Figure 5 shows the fractions collected from the setup.

Figure 5: The collected fractions of product streams from the setup during continuous operation. To the left is the aqueous waste from the decanter, at the center is the organic phase containing dehydrated product **5** and to the right is the crystalline Melitracen HCl **6** API and the mother liquid.

Operation of Full Flow Setup

The final flow setup, as illustrated in Figure 4, was operated for 300 minutes under steady state conditions. The experiment was terminated at the point of complete utilization of the 2 M HCl (Et_2O). For the first 30 minutes the setup was not in steady state due to a tube burst and fittings

around the IR flow cell, but a steady state was achieved shortly after replacement of the broken fittings. The tube burst was a result of a clog formed from Grignard reagent reacting with residual water in the IR flow cell from previous cleaning. The flow rate of the system is given in Table 2 and Table 3 provides the residence times in the important parts of the reactor.

Table 2: The reactor configurations and residence times, along with important observations, for the Melitracen HCl 6 synthesis as operated with the flow setup (Figure 4).

Reactor part	Flow Rate (mL/min)	Reactor Volume (mL)	Residence Time (s)	Observation
Coil 1	4.5	4.95	66	Deep red color from reaction. Temperature higher than ambient, lower than the boiling point of THF.
Coil 2	5.5	1.98	21.6	Temperature is above the boiling point of THF, 100 psi suppress boiling. Stream becomes transparent with a white solid that disappears into an one-phase system. pH < 2
Coil 3	8.0	0.99	7.4	One-phase system pH < 2
Coil 4	9.9	1.98	6.0	Two-phase system pH > 10
Decanter (Org/Aq)	9.9 (4.5/5.4)	100	606.1	Two-phase system pH > 10

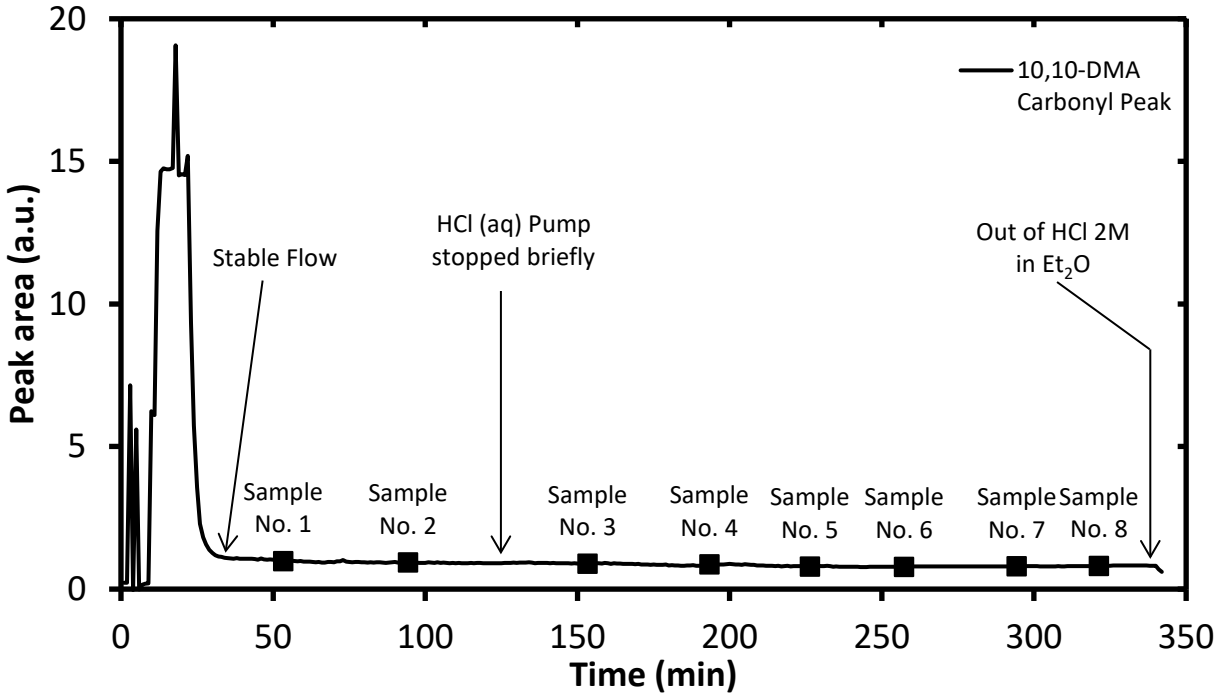
Table 3: The flow rates and concentrations of the different reactants used in the flow setup.

Reactants	Flow rate (mL/min)	Concentration (M)	Equivalence to 10,10-DMA **1**
10,10-DMA **1**	2.0	1.8	1.0
DMPC-MgCl **2**	2.5	1.5	1.05
HCl (aq)	1.0	12 (37%)	3.33
AcOH (aq)	2.50	7 (40%)	4.86
NH_3 (aq)	1.9	13.4 (25%)	7.07

HCl (Et_2O)	2.25	2	1.25

313

314 An IR flow cell was placed after coil 1 and was used to follow and ensure that full conversion
315 of 10,10-DMA **1** was achieved. Figure 6 shows the carbonyl peak of the 10,10-DMA **1** as it
316 progressed throughout the experiment. The trend line absorbance intensity of the peak is based
317 on area to zero baseline for the IR region of 1610-1580 cm^{-1} and is given in arbitrary units. The
318 off-line HPLC data in Table 4 confirms full conversion of 10,10-DMA **1**. The replacement of the
319 tubing caused an exposure of the magnesium alkoxide **3** to the surrounding atmosphere (i.e.
320 moisture in the air), resulting in the deposit of magnesium salts on the IR diamond window.
321 Despite an attempt to clean the window, some deposit was still present, causing the small offset
322 from the zero baseline, which explains why zero is not achieved.



323

324 **Figure 6:** The IR data on the flow setup run, following the peak of the carbonyl functional group
325 of 10,10-DMA (1) and the reference samples for off-line HPLC analysis given in Table 4. Steady

state conditions were achieved after 30 minutes; the initial 30 minutes of unstable flow were related to bursting and replacing of tubing and fittings.

A portion of the Melitracen HCl (**6**) was collected by filtration in a Büchner funnel, washed with THF and dried in a vacuum oven at 50 °C for 24 hours. The product was subjected to complete release analysis for the API and all product attributes were found to be within specification. A total of 300 g of dry Melitracen HCl (**6**) was isolated from the flow setup, requiring a consumption of approximately 240 g 10,10-DMA (**1**) starting material.

Table 4: The HPLC samples, where samples were collected from the aqueous waste stream of the decanter, the crystallized Melitracen HCl (**6**) and the mother liquid, and a few from the organic phase of the decanter.

Sample No.	Compound	Crystallized Product (Area%)	Mother Liquid (Area%)	Decanter Aqueous (Area%)	Decanter Organic (Area%)
1	Melitracen (**5** or **6**)	100	97.65	62.0	No sample
	Alcohol (**4**)	nd	nd	38.0	
	10,10-DMA (**1**)	nd	2.1	nd	
	Other Impurities	nd	0.2	nd	
2	Melitracen (**5** or **6**)	100	97.8	37.8	No sample
	Alcohol (**4**)	nd	nd	62.1	
	10,10-DMA (**1**)	nd	2.0	nd	
	Other Impurities	nd	0.2	nd	
3	Melitracen (**5** or **6**)	100	96.3	20.5	No sample
	Alcohol (**4**)	nd	nd	79.5	
	10,10-DMA (**1**)	nd	3.5	nd	
	Other Impurities	nd	0.2	nd	
4	Melitracen (**5** or **6**)	100	99.0	nd	No sample
	Alcohol (**4**)	nd	nd	100	
	10,10-DMA (**1**)	nd	0.8	nd	
	Other Impurities	nd	0.2	nd	
5	Melitracen (**5** or **6**)	99.9	99.1	nd	No sample
	Alcohol (**4**)	0.1	nd	100	

	10,10-DMA (**1**)	nd	0.7	nd	
	Other Impurities	nd	0.2	nd	
6	Melitracen (**5** or **6**)	100	99.3	nd	100
	Alcohol (**4**)	nd	nd	100	nd
	10,10-DMA (**1**)	nd	0.5	nd	nd
	Other Impurities	nd	0.2	nd	nd
7	Melitracen (**5** or **6**)	100	39.8	39.3	99.8
	Alcohol (**4**)	nd	60.2	60.7	0.2
	10,10-DMA (**1**)	nd	nd	nd	nd
	Other Impurities	nd	nd	nd	nd
8	Melitracen (**5** or **6**)	100	56.4	26.2	100
	Alcohol (**4**)	nd	43.6	73.8	nd
	10,10-DMA (**1**)	nd	nd	nd	nd
	Other Impurities	nd	nd	nd	nd

Conclusions

A full redesign of a current batch synthesis to a full flow setup has been possible, from the starting material to the final salt crystallization of the active pharmaceutical ingredient, Melitracen HCl. The flow process was significantly simplified compared to the batch process, with removal of a phase separation and usage of tetrahydrofuran (THF) only as a solvent compared to the previous toluene-THF solvent mixture. All synthetic steps were carried out at ambient temperature, whereas routine batch production requires active heating (up to 50°C) and cooling in several steps. The crystallization of the Melitracen HCl was proven possible in THF with 2 M HCl in diethyl ether (Et_2O) and eliminated a solvent swap to ethanol. The crystallization was not optimized and would most likely be done with HCl gas, with an expected additional gain in yield from the lower volume of solvent. The isolated yield in the given study was approximately 85%. The phase separation achieved with the decanter was higher than 99% product in the organic phase, with a HPLC purity of greater than 99%. The isolated Melitracen HCl was analyzed in accordance with the in-house release methods required for current batch

production and all measurements were in accordance with requirements. A production of 60 g/h of isolated Melitracen HCl can be achieved with the flow setup. Furthermore, the setup demonstrated great robustness towards fluctuations in reactant streams. The one-step hydrolysis and dehydration could potentially be applicable for other Grignard additions, as could the subsequent decanter phase separation.

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