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Supplementary Information

Continuous Purification of Active Pharmaceutical Ingredients Utilizing Polymer Membrane Surface Wettability

Joseph Imbrogno[a], Luke Rogers[a], Dale A. Thomas[b], Klavs Jensen[a,c,*]

[a]Department of Chemical Engineering, Massachusetts Institute of Technology, Cambridge, MA, 02139, USA. E-mail: kfjensen@mit.edu.
[b]Department of Mechanical Engineering, Massachusetts Institute of Technology, Cambridge, MA, 02139, USA
[c]Department of Materials Science and Engineering, Massachusetts Institute of Technology, Cambridge, MA, 02139, USA

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1. Materials

Hexane (≥95%), heptane (≥99%), isopropyl alcohol (IPA), acetone (≥99.9%), toluene (99.9%), ethyl acetate (≥99.5%), methanol (≥99.9%), N-Methyl-2-pyrrolidone (NMP, anhydrous, 99.5%), potassium hydroxide, ammonium chloride, sodium chloride, dimethylformamide (DMF, anhydrous 99.8%), and dichloromethane (DCM, ACS Reagent Grade) were purchased from Sigma Aldrich. Milli-Q water was generated and used for all experiments. All chemicals were used as received, without further purification.

PTFE membranes (47 mm diameter, 0.1 μm pore size, polypropylene support) were purchased from Sterlitech Corporation. Glass microfiber membranes (Whatman, 47 mm diameter, GF/A, nominal particle retention of 1.6 μm) were purchased from General Electric. PFA film (1 mil thickness) was purchased from McMaster Carr. Both membranes and PFA film were cut to the appropriate size to fit into the separator module.

2. Experimental Methods

2.1. Solvent Ramping Experiments to Determine Maximum Flow Rates

The first set of solvent ramping experiments involved flowing 2 solvents (aqueous and organic) at the same flow rate, while slowly ramping the flow rate of a third solvent in a step-wise procedure. The third solvent was chosen to be soluble in both the aqueous and organic phases. For the water-toluene-acetone system, the water and toluene flow rates were held at 1.00 mL/min, while the acetone flow rate was increased 0.10 mL/min per step, up to a maximum of 1.00 mL/min. The system was equilibrated for 5 min in between each step. A sample was collected after equilibration at each step (**Fig. S1**). The water-ethyl acetate-acetone (**Fig. S2**) procedure was identical.

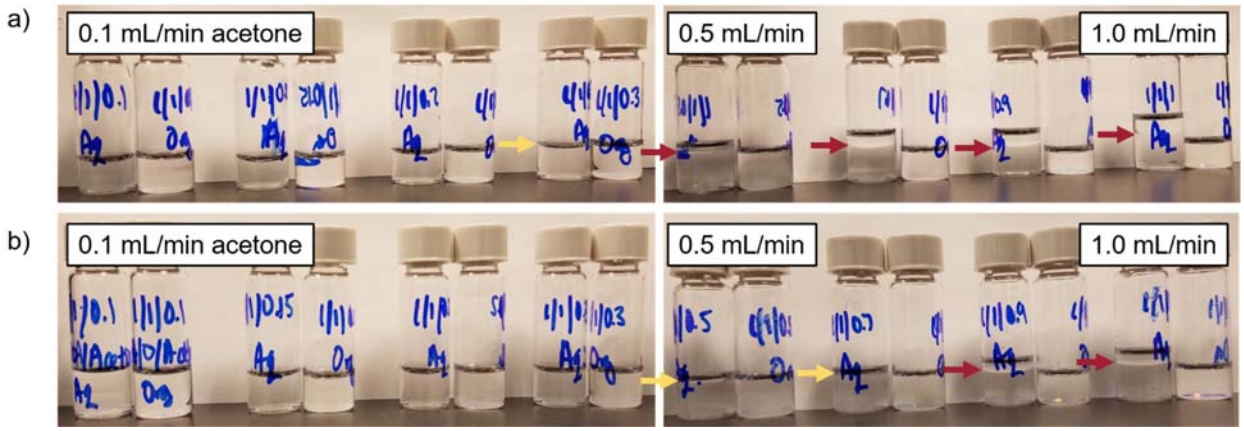

Fig. S1. Samples collected at each step during ramping of acetone flow rate in water-toluene-acetone system, where a) is for a one PTFE membrane system and b) is for a system containing both a PTFE and a glass microfiber membrane. Yellow arrows indicate when a small amount of retention was first observed (small droplets) and red arrows indicate when a layer of retention was formed. Failure occurred at 0.50 mL/min for the 1 membrane system and 0.90 mL/min for the 2 membrane system,

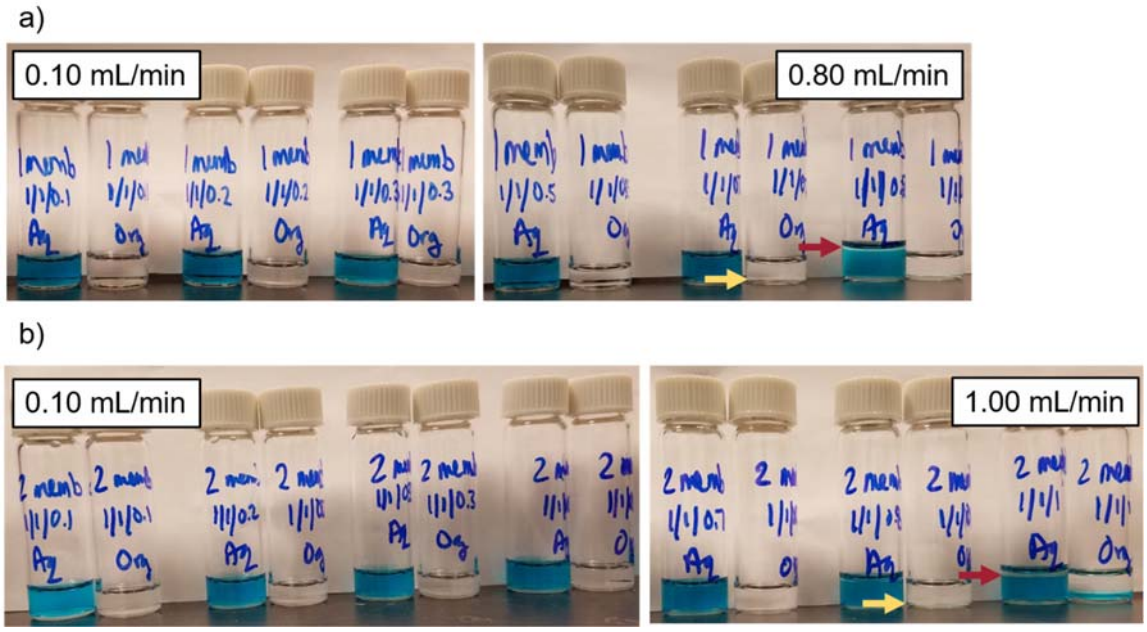

Fig. S2. Samples collected at each step during ramping of acetone flow rate in water-ethyl acetate-acetone system, where a) is for a one PTFE membrane system and b) is for a system containing both a PTFE and a glass microfiber membrane. Yellow arrows indicate when a small amount of retention was first observed (small droplets) and red arrows indicate when a layer of retention was formed. The water phase was dyed blue for these experiments. Failure occurred at 0.80 mL/min for the 1 membrane system and at 1.00 mL/min for the 2 membrane system.

2.2. Solvent Ramping Experiments to Determine Minimum Glass Membrane Size

The surface area of the glass microfiber membrane plays a large role in enhancing the separation performance, therefore, a separate series of ramping experiments were conducted in order to determine the minimum size of the glass microfiber membrane. Here, all 3 solvent flow rates were held constant, while the size of the glass microfiber membrane was decreased in a step-wise fashion. The 3 solvents used here were water-hexane-isopropyl alcohol (IPA) and their flow rates were 1.00, 1.00, 0.50 mL/min, respectively. The flow rate of IPA was chosen such that it was above the point at which a one membrane system failed (PTFE membrane only), but below the point at which the two membrane system failed (PTFE and glass microfiber membranes). The glass microfiber membrane length was varied from 2.5 cm to 0.5 cm by decreasing the length 0.5 cm at each step with a constant width of 0.5 cm for all experiments. It was determined that the smallest membrane size that still achieved complete separation was 1.0 cm x 0.5 cm, below which a small amount of breakthrough was observed. This occurred when the surface area of the glass microfiber membrane becomes too small and its effects are overcome by convective flow.

2.3. Gas Chromatography Flame Ionization Detector (GC-FID) Analysis of Ramping Experiments

GC-FID spectra were collected in order to quantify the concentration of IPA in each sample of the water-hexane-IPA system after equilibrium had been reached. All samples were prepared by diluting 500 µL of each sample in 500 µL of toluene. The GC-FID samples were analyzed using an Agilent 7890A system equipped with a J&W 122-1334 column (30 m x 250 µm x 1.4 µm) with a flow rate of 1.5 mL/min. The temperature ramp was as follows: initial temperature of 60°C for 0.5 min, ramp at 45°C/min to 90°C and hold for 2 min., ramp at 40°C/min to 175°C (no hold), and finally ramp at 30°C/min to 250°C (no hold). The experimental spectra were compared with a calibration curve that was prepared by diluting IPA in toluene at different concentrations (**Fig. S3**). The actual

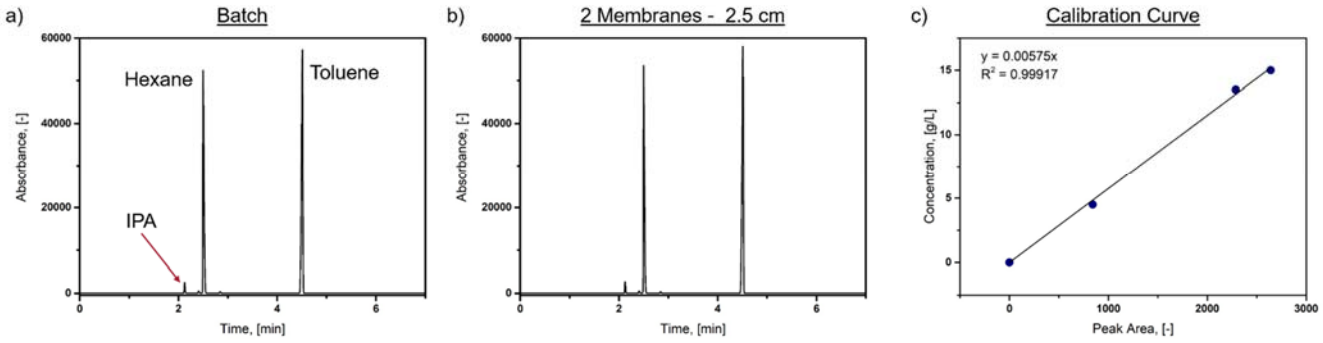

Fig. S3. Representative GC spectra for the water-hexane-IPA system using a) a batch extraction and b) separation in flow using 2 membranes (PTFE and glass microfiber membrane), where the glass membrane was 0.5 cm x 2.5 cm. Samples were diluted 1:1 in toluene, resulting in the toluene peak observed at 4.5 min. A calibration curve shown in c) was used to calculate the actual concentrations and then doubled accounting for the 1:1 dilution in toluene.

Table S1. Volumes and Volumetric flow rates used for data shown in **Fig. S3**.

Number of Membranes	Sample	IPA [mL, mL/min]	Water [mL, mL/min]	Hexane [mL, mL/min]
0	Batch	0.50	1.00	1.00
1 Glass	Batch w/ glass	0.50	1.00	1.00
1 PTFE	Flow	0.45	1.00	1.00
1 PTFE, 1 glass	0.5x1.5 cm glass	0.49	1.00	1.00
	0.5x2.0 cm glass	0.49	1.00	1.00
	0.5x2.5 cm glass	0.50	1.00	1.00

concentrations were then back-calculated, accounting for the toluene dilution factor. The volumes or volumetric flow rates used for these experiments are shown in **Table S1**.

Based on the GC-FID results, there was no statistical difference in equilibrium concentration of IPA between all samples tested (batch and continuous), as shown in **Fig. S4**. This allows for facile modeling and scale-up of the process without the need for non-equilibrium based corrections.

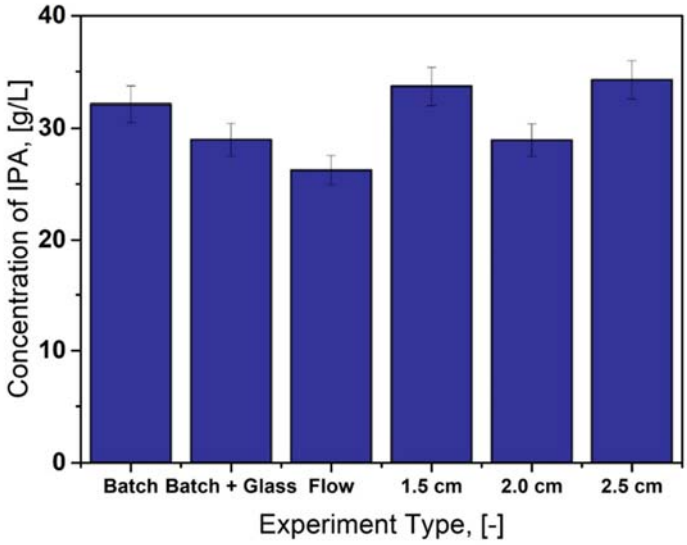

Fig. S4. Concentration of IPA in the hexane phase from the water-hexane-IPA system tested in both batch and flow, with and without a secondary glass membrane added. The equilibrium concentration of IPA in the organic phase does not change with the addition of the glass membrane. Each system was measured in triplicate and error bars represent ± 5% standard deviation to account for small errors due to manual injection into the GC.

2.4. Fundamental Wettability Experiments

In order to confirm that the glass microfiber membranes were actually being wet by the aqueous phase and thereby enhancing the separation, a simple apparatus was constructed. A short length of ¼" OD PFA tubing was connected to a piece of 1/8" OD tubing, which had solvents being pumped through it, and left open to the atmosphere at the opposing end (**Fig. 3a**). Small pieces of PTFE and glass microfiber membranes were placed into the open end of the ¼" tubing. The formats tested can be seen in **Fig. S5** as

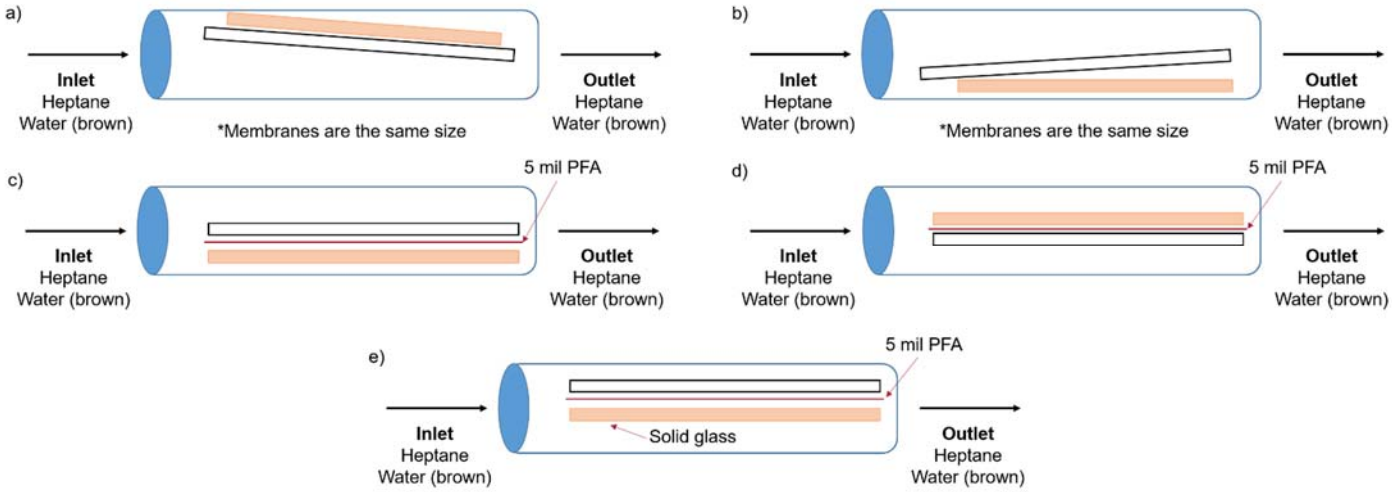

Fig. S5. Different configurations used to test the wettability of the glass microfiber membrane by the aqueous phase. The placement of the two membranes varied where a) glass membrane was on top of PTFE membrane without a divider, b) PTFE was on top of the glass membrane without a divider, c) PTFE was on top of the glass membrane separated by a 5 mil PFA film, d) the glass membrane is on top of the PTFE membrane separated by a 5 mil PFA film, and e) same as c) except the glass membrane was replaced with solid glass (lower surface area).

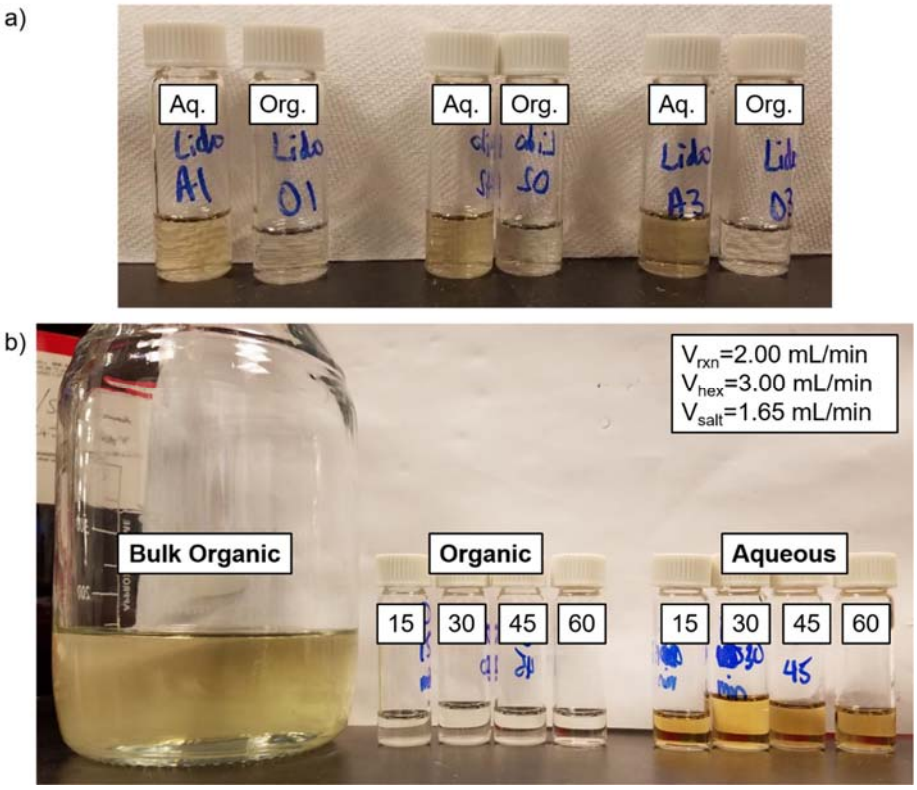

Fig. S6. Lidocaine samples collected after LLE and separation for a) low flow rates (0.60/0.50/0.90 mL/min rxn/aq./org.) and high flow rates. The bulk organic sample shown in b) was collected over 1 hr. of run time. Complete phase separation was achieved for all samples.

well as short videos in **Supplemental Videos**. A mixture of water and heptane was then pumped into the 1/8” tubing in slug flow and allowed to contact the two materials placed in the large OD tubing. This format was also tested with a solid glass sheet, instead of a glass microfiber membrane, in order to observe the effects of lower surface area on performance. This setup was also able to separate the two phases, but only up to a lower flow rate than the porous glass microfiber membrane.

2.5. LLE and Phase Separation of Lidocaine, Diazepam, Atropine, and Diphenhydramine

All 4 API's have been synthesized previously and are described elsewhere.[1-4] Each purification process involved the mixing of a crude reaction stream with one or more solvent streams in order to isolate the product in the organic phase and remove impurities, followed by phase separation using the membrane separator. Each process is described briefly here, as well as shown schematically in **Fig. 4**.

Crude Lidocaine (40 mg/mL) containing water, methanol, NMP, and KOH (water:MeOH:NMP ratio (v/v) of 1:1:0.87) at 0.60 mL/min was mixed with 0.50 mL/min saturated sodium and ammonium chloride solution as well as 0.90 mL/min hexanes in a cross. This mixture then passed through 100 cm of PFA mixing tubing (1/16" OD, 1/32" ID) where LLE occurred in slug flow. It then passed through a membrane separator using a 0.1 μm PTFE membrane, a glass microfiber membrane, and a 1 mil PFA diaphragm. Samples of both the aqueous and organic were collected and analyzed using HPLC (**Fig. S9a**). These flow rates were then scaled up, while maintaining the same flow rate ratio, to a total flow rate that is much closer to actual production scale. The crude lidocaine, salt solution, and hexanes flow rates were scaled to 2.00, 1.65, and 3.00 mL/min, respectively. The LLE tubing length was not increased, therefore a shorter residence time for mixing was utilized for this system. Collected samples of both the low flow rates and scaled up flow rates are shown in **Fig. S6**.

Crude Diazepam (25 mg/mL) containing methanol, water, and NMP (water:MeOH:NMP ratio (v/v) of 1:1:1.37) at a flow rate of 1.08 mL/min was mixed with saturated NaCl solution at 0.98 mL/min and ethyl acetate at 1.94 mL/min in a cross. The

mixture passed through 100 cm of mixing tubing for LLE again and then into an identical separator as described for Lidocaine. Since a large amount of retention was present, the aqueous stream was then passed into another separator (membrane components) for further phase separation. Therefore, the organic outlet from the first separator was collected separately since it contained Diazepam. The aqueous outlet was passed directly to the inlet of the second separator where complete phase separation occurred. Samples were collected throughout the run (**Fig. S7**) and analyzed using HPLC (**Fig. S9b**).

Crude Atropine (30 mg/mL) containing water and DMF (water:DMF ratio (v/v) of 1:0.16) at 0.67 mL/min was mixed with toluene at 0.15 mL/min in a tee and sent directly into a separator where the toluene phase contained the impurities and the aqueous phase contained the product. The outlet aqueous phase was then mixed with DCM at 0.15 mL/min and sent into a second separator where Atropine was isolated in the organic

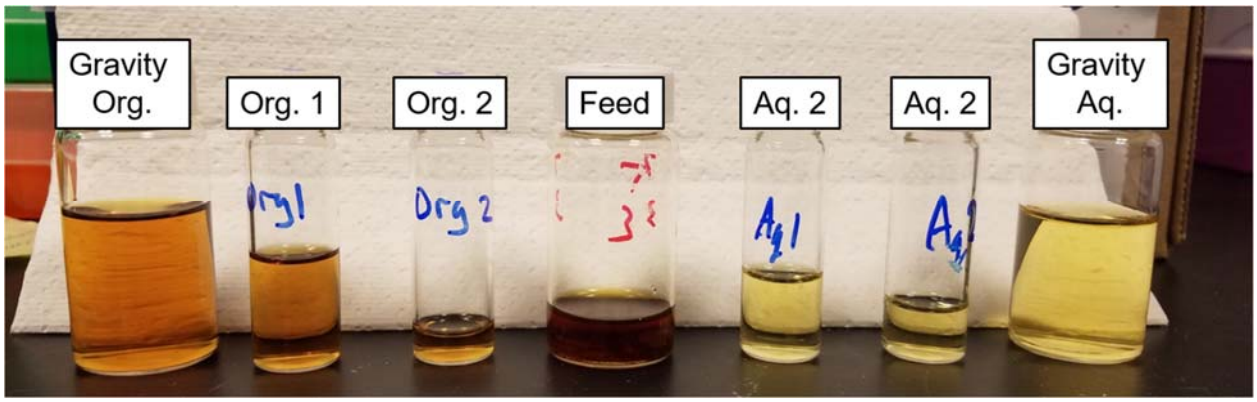

Fig. S7. Samples collected from both organic outlets and the second aqueous outlet of the two membrane separators. Since some retention was observed in the first module, the aqueous outlet was passed directly into a second separator, which achieved complete separation. Therefore, complete separation was achieved for all samples that were collected. The separation was compared with a gravity separation (using same procedure, except in batch) and were found to be identical. Gravity separated samples are shown on the far left and far right in the picture.

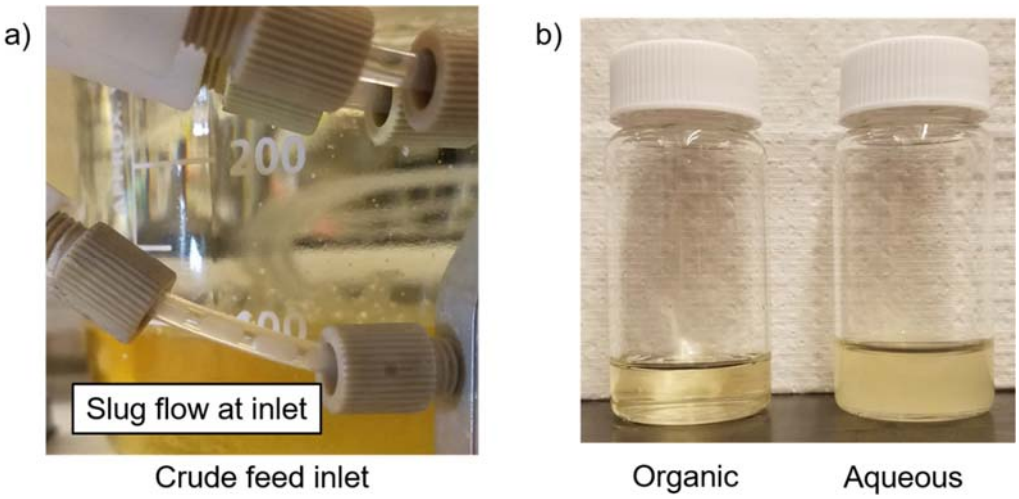

Fig. S8. Since Atropine is not a stable product, the separation was carried out during the synthesis. A picture taken of the inlet flow and aqueous and organic outlets is shown in a) and representative samples taken at the outlet of the separator are shown in b). Complete phase separation was achieved in all samples that were collected.

phase containing DCM and DMF and the aqueous phase contained water and DMF. Samples were collected throughout the run (**Fig. S8**) and analyzed using HPLC (**Fig. S9c**).

Crude Diphenhydramine (190 mg/mL) containing water, NaOH, dimethylaminoethanol, and chlorodiphenylmethane (water:dimethylaminoethanol:chlorodiphenylmethane ratio (v/v) of 1:0.15:0.09) at a flow rate of 3.45 mL/min was mixed with saturated Milli-Q water at 1.39 mL/min and hexanes at 1.39 mL/min in a cross. The mixture passed through a packed bed and then into two identical separators, with the same membrane components as per Lidocaine, configured in parallel. Complete phase separation was achieved out of both separators. Samples were collected throughout the run and analyzed using HPLC (**Fig. S9d**).

2.6. HPLC Methods for Analyzing API's

All samples were analyzed using the corresponding USP monograph for each API. The following USP monographs were used: Lidocaine hydrochloride (pg. 4561),

Diazepam (pg. 3442), Atropine sulfate (pg. 2638), and Diphenhydramine Hydrochloride (pg. 3526) from USP 39, 2016. HPLC spectra for all 4 APIs are shown in **Fig. S9**. The standard is shown as a dotted black line, the aqueous phase is a solid red line, and the organic phase is a solid blue line.

Directly after the separation, the aqueous and organic phases were collected separately. The aqueous phases were all analyzed directly at this step as they were soluble in the USP required mobile phases for each API. However, since several of the organic phases were not soluble in their mobile phases at this step, they were not analyzed until after final purification steps. This only applies to diazepam, atropine, and diphenhydramine, but not lidocaine. Both outlets from the lidocaine separation were analyzed directly after separation and are shown in Fig S9a. Therefore, lidocaine is representative of exactly what is coming out of the separator directly after purification. There are several very minor impurities present in the organic spectrum in this case due to this fact.

For the other 3 APIs, it is clear that no API is present in each aqueous phase, as indicated by the lack of an absorbance signal in each aqueous phase at the same elution time as the standards (~5.5 min for diazepam, ~9.5 min for atropine, and ~5 min for diphenhydramine). Since these aqueous phases were analyzed directly after the separation, that means that 100% of each API was extracted into the organic phase.

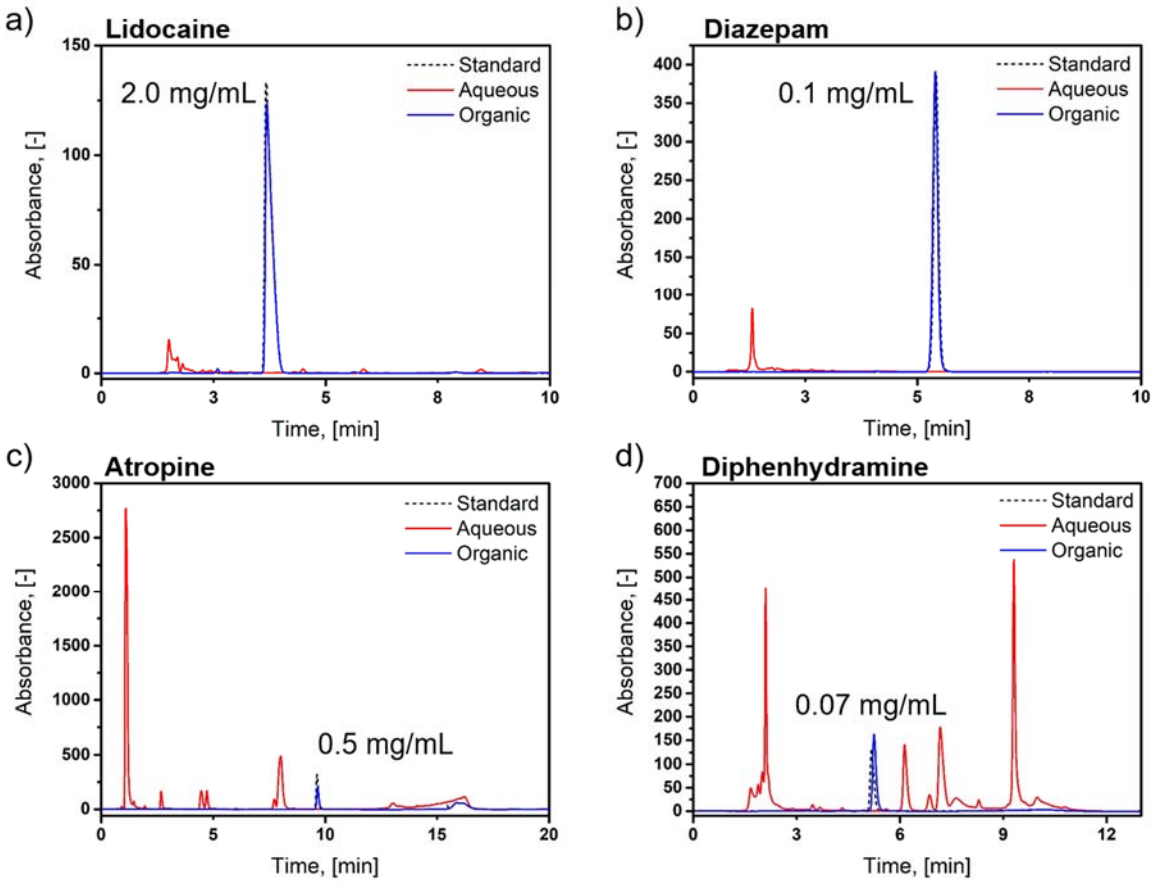

Fig. S9. HPLC spectra for a) lidocaine, b) diazepam, c) atropine and d) diphenhydramine. Product peak positions eluted at the following approximate times: a) 4 min, b) 5.5 min, c) 9.5 min, and d) 5.5 min. The corresponding concentrations for each standard are as follows: lidocaine = 2 mg/mL, diazepam = 0.1 mg/mL, atropine = 0.5 mg/mL, diphenhydramine = 0.07 mg/mL.

2.7. Membrane Separator Description

The membrane separators used herein have been published previously, but are also described here.[5-7] The pressure is controlled using a thin chemically compatible perfluoroalkoxy alkane (PFA) polymer diaphragm that acts to modulate the pressure between the aqueous and organic sides of the membrane. Different diaphragm thicknesses allow one to control the pressure the diaphragm exerts on the system, known as P_{dia}. The upper and lower bounds for operating this system while achieving complete

phase separation correspond to the capillary and permeation pressure, respectively. This means the capillary pressure must be greater than the diaphragm pressure and the diaphragm pressure must be greater than the permeation pressure. The capillary (P_{cap}) and permeation (P_{per}) pressures depend largely on the geometry of the membrane and the physical properties of the mixture. One of the most important parameters being the interfacial tension between the two phases, since it cannot be varied without chemical additives or changing solvents. The governing equations for P_{cap} and P_{per} are shown in **Eqs. S1** and **S2**, respectively.

$$P_{cap} = \frac{2\gamma\cos(\theta)}{R_{pore}} \quad \text{Eq. S1}$$

$$P_{per} = \frac{8\mu_{per}\left(\frac{Q_{per}}{n_{pores}}\right)L_{pore}}{\pi R_{pore}^4} \quad \text{Eq. S2}$$

It is important to stay within the operating range of the system; otherwise incomplete phase separation will occur. If P_{dia} is too high ($P_{dia} > P_{cap}$), then there will be breakthrough of the aqueous phase into the permeated organic phase. If P_{dia} is too low ($P_{dia} < P_{per}$), then there will be retention of the organic in the aqueous phase. The capillary and permeation pressures are only the theoretical upper and lower limits, respectively, of the system, therefore, it is important to note that the actual operating range where complete separation will occur might exist in a smaller region when using the real system. This is due to the fact that some of the parameters are estimated. This is a result of the pore size distribution in the membrane, the contact angle and interfacial tension of the

mixture are difficult to measure exactly, and the exact composition of the mixture will vary, which affect these physical properties.

Since the applied pressure is intrinsically linked with the phase separation performance, we are limited to operating at a set maximum pressure (P_{dia}). Therefore, these membranes are not being operated at their maximum flux capabilities. In other words, the inlet volumetric flow rate of the organic phase will be equal to outlet organic flow rate after phase separation, up to the maximum total flow rate possible for these modules. The maximum total flow rate that these modules are capable of separating for a binary mixture is 12 mL/min. Since only the organic phase will permeate (with complete phase separation), the maximum flux that could be achieved, for an ideal binary mixture, using these modules is ~3 mL/cm^2*min (~1800 LMH). However, for complex multi-component mixtures like those used here, the maximum flux is closer to 0.4 mL/cm^2*min (240 LMH).

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