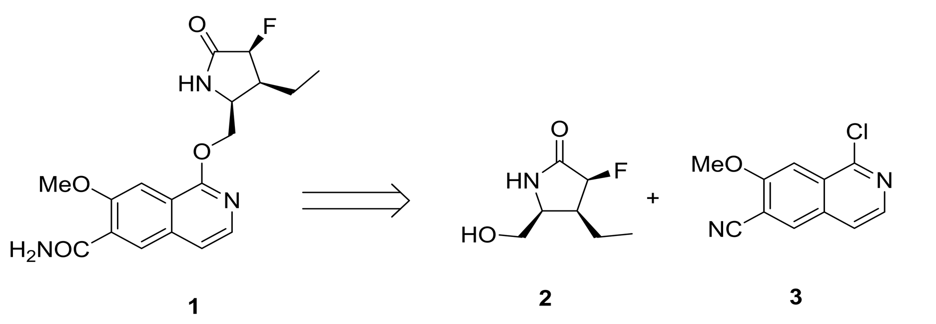
Development and Scale Up of an End-to-End Process (Enolate Oxidation)

Continuous Production of Anhydrous tert-Butyl Hydroperoxide in Nonane Using Membrane Pervaporation and Its Application in Flow Oxidation of a g-Butyrolactam - **OPRD 2018** https://pubs.acs.org/doi/ipdf/10.1021/acs.oprd.8b00083

Development…

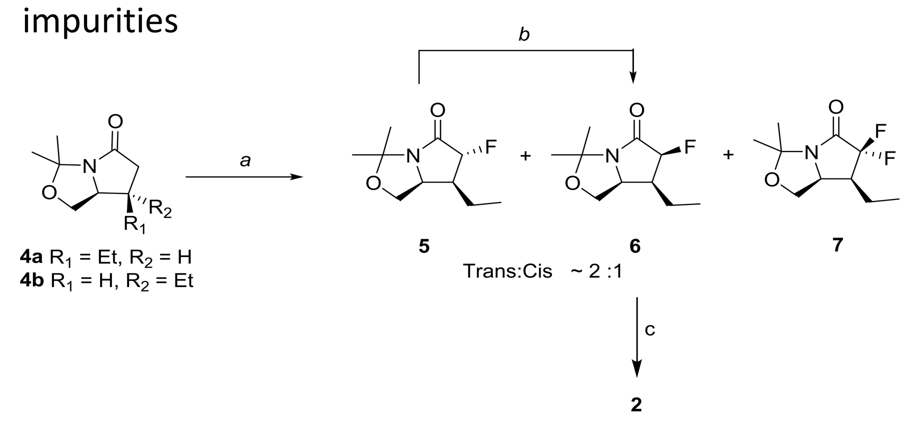
Interleukin-1 Receptor Associated Kinase (IRAK 4)

- Therapeutic target: dysregulated inflammation diseases (e.g. systemic lupus erythematosus {SLE}, rheumatoid arthritis)
- **1**; potent and selective IRAK4 inhibitor



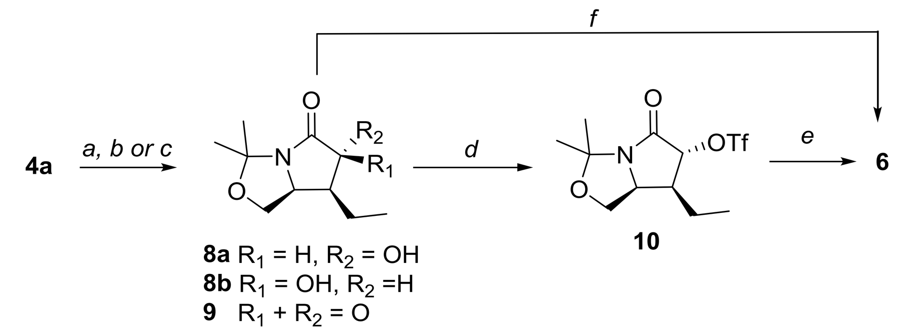
Active Pharmaceutical Ingredient (API) synthesis from chiral lactam (2)

- Early synthesis of **2** – electrophilic fluorination of **4a** via enolation & reaction with N-fluorobenzenesulfonimide resulting in a mixture of diastereomers & undesirable impurities

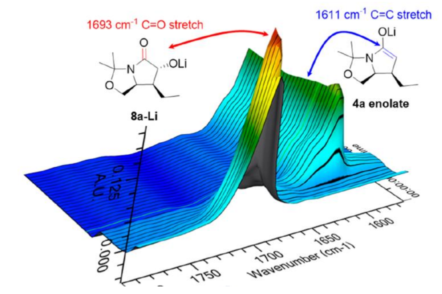


New approach for synthesis of chiral lactam (2)

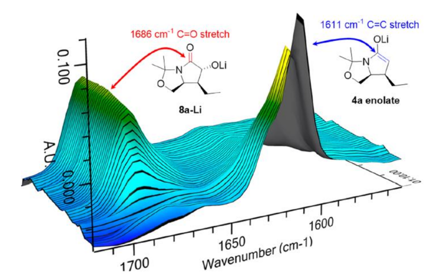
- Diastereoselective synthesis via preparation of hydroxylated lactam **8a**
  - Hydroxylation of carbanions by transfer of electrophilic Oxygen atom
  - Highly diastereoselectivity hydroxylation of **4a** in greater than 30:1 (**8a/8b**) ratio.



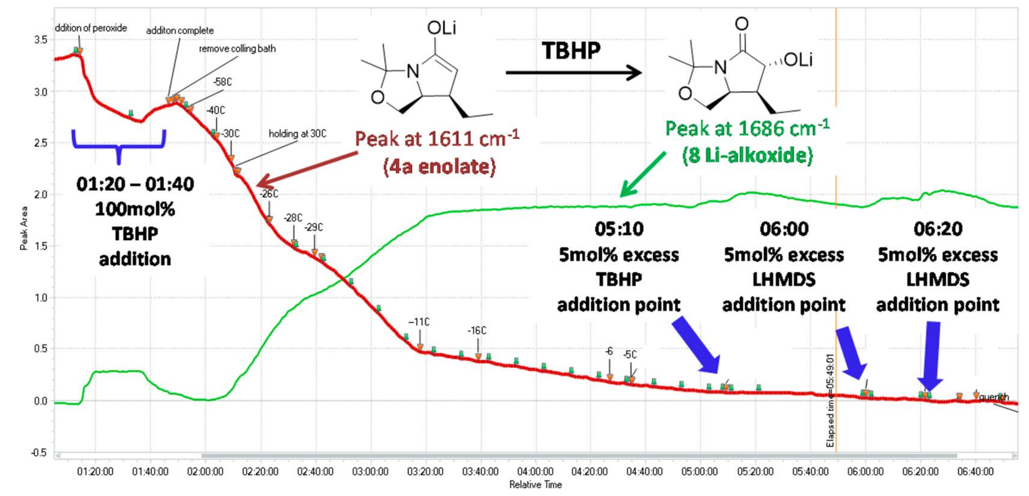
Hydroxylation using: Lithium t-butyl peroxide (LiOOtBu) or LHMDS and tert-Butyl hydroperoxide (TBHP)



IR bands during enolate formation



IR bands during oxidation reaction



IR spectrum after TBHP addition

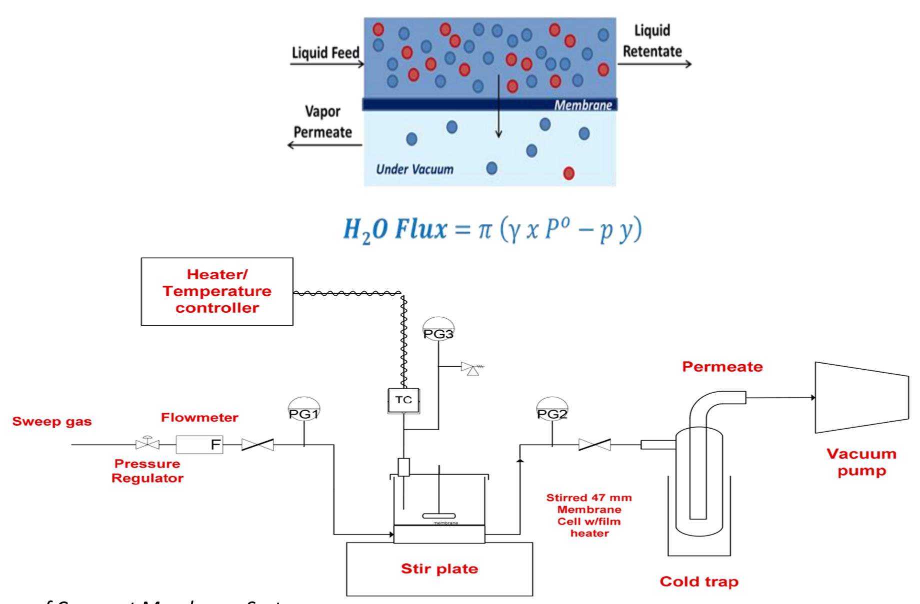
- TBHP provided the best impurity profile for this reaction.
- Develop a scalable process using TBHP (Safety concern!)

Use of TBHP for industrial process?

- **Challenge:**
  - TBHP explosive risk on transportation and storage; not available at bulk scale then roadblock for scale up
  - TBHP needs to have **less than 0.20% water** to avoid side reactions during the oxidation
- **Solution:**
- Molecular Membrane for Water Extrusion
  - Low hold up volume; below DSC onset temp; continuous and highly reproducible.

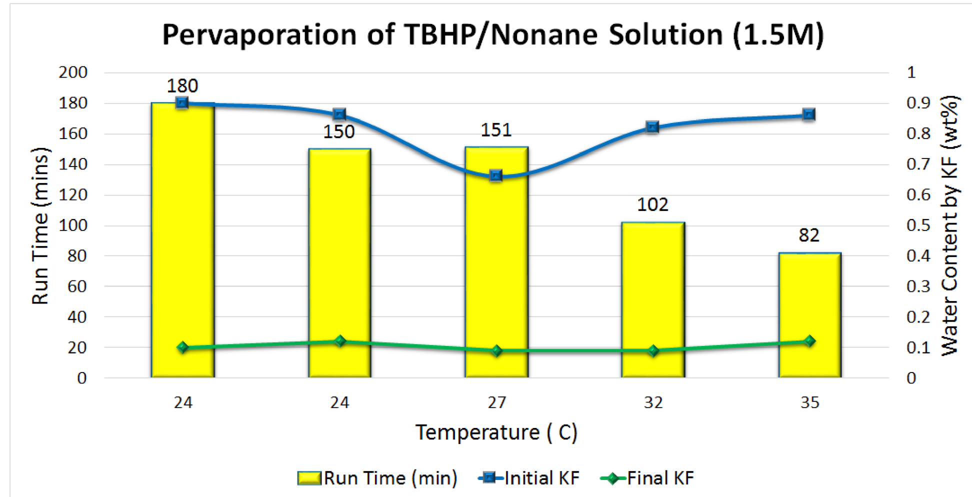
Pervaporation

Pervaporation Principle and Lab Equipment…



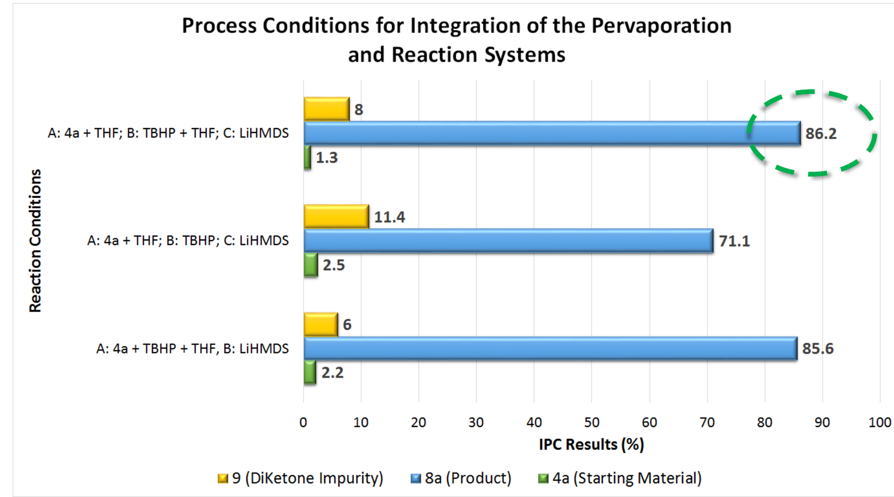
* Courtesy of Compact Membrane Systems

Pervaporation Tests in the Lab…



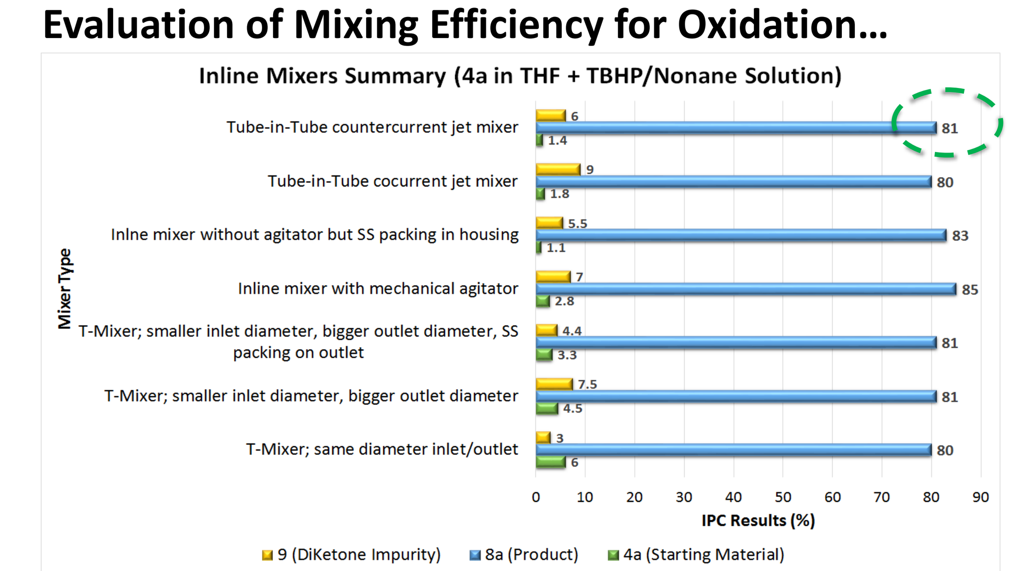
Temperature as a driver to reduce run time and still achieve acceptable KF on TBHP/Nonane solution

Evaluation of Reagent's Order of Addition…



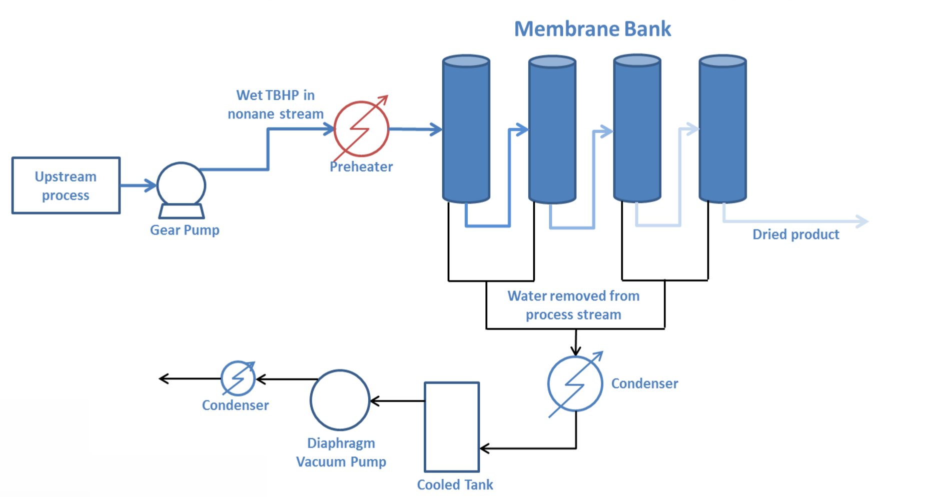
Dilute TBHP/Nonane solution with THF prior to Oxidation reaction via inline mixing

Evaluation of Mixing Efficiency for Oxidation…



Residual 4a more difficult to purge downstream, 9 (Diketone Impurity) easily rejected. Inline Mixer selected based on simplicity (less moving parts) and easy scalability; then **tube-in-tube countercurrent jet mixer** selected

Pervaporation Rig for Continuous TBHP Drying



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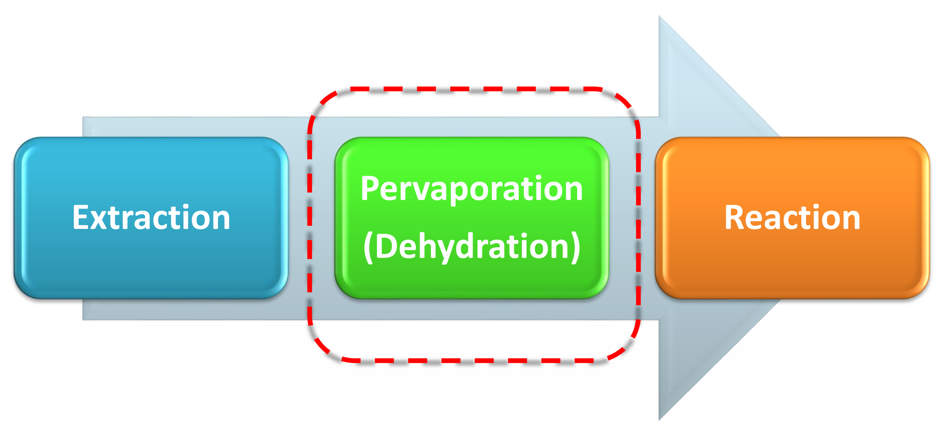
Pervaporation Rig

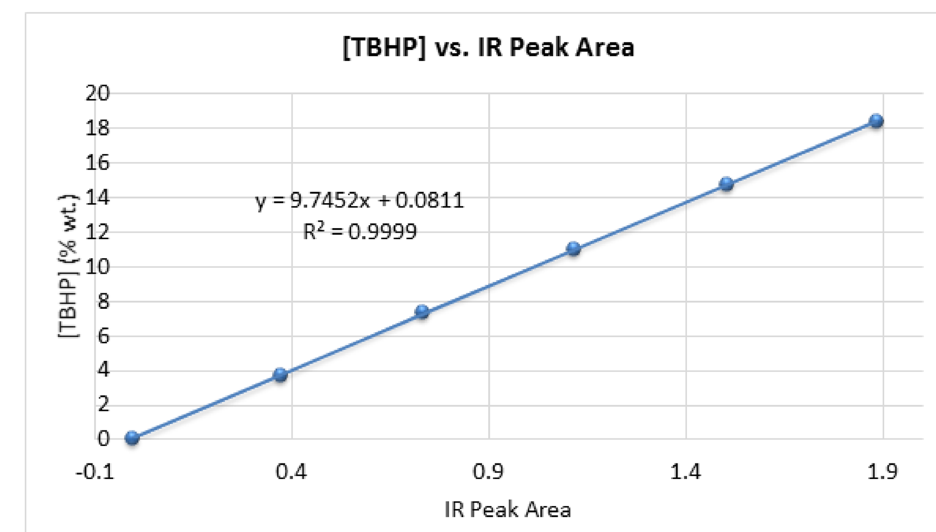
* Courtesy of Compact Membrane Systems

Integration of Pervaporation System to the Continuous Oxidation Process



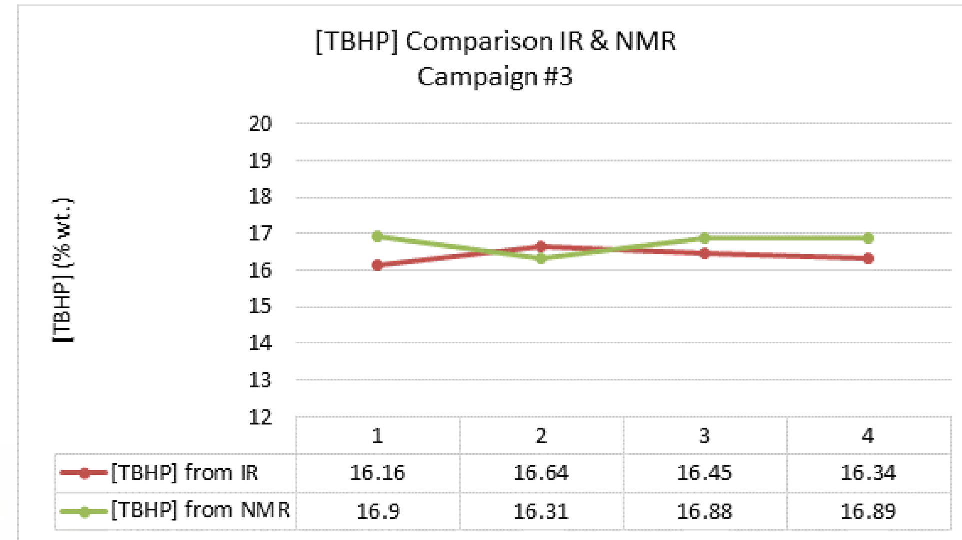
Requirement for Commercial Scale: Pervaporation system capable of continuously reducing the water content of a 1.5M TBHP + Nonane solution to 1100 ± 200 ppm at a rate of 100 mL/min.

Process Analytical Technology (PAT) Integration



IR Calibration curve for TBHP Concentration

Process Analytical Technology (PAT) Integration (cont.)



Average [TBHP] via **IR 16.4% wt.**; Average [TBHP] via **NMR 16.7% wt.**

Scale Up…

Integration of Operational Units

Operational Unit	Campaign 1	Campaign 2	Campaign 3[1]
Extraction	Batch	Continuous	Continuous
Dehydration	Batch	Continuous	Continuous[2]
Reaction	Continuous (PFR + CSTR)	Continuous	Continuous[3]

1. All 3 operational units connected
2. Use of react-IR to measure TBHP content downstream of pervaporation system
3. Inline mixer prior to PFR to enhance mixing and reduce Diketone impurity formation

Comparison of Plug Flow Reactors (PFR) at Different Scales

Scale	L/D	Reactor Volume (L)	Residence Time (mins)	Re
Lab	46,279	0.360	75.2	74
Campaign 1	10,667	28.27	70	885
Campaign 2	20,000	53.01	73	1593

- Higher L/D reduces axial dispersion and promotes radial dispersion (ideal PFR)
- Laminar fluid regime (Reynolds number (Re) < 2100) maintained at all scales; mixing of reagents governed by diffusion in the radial direction

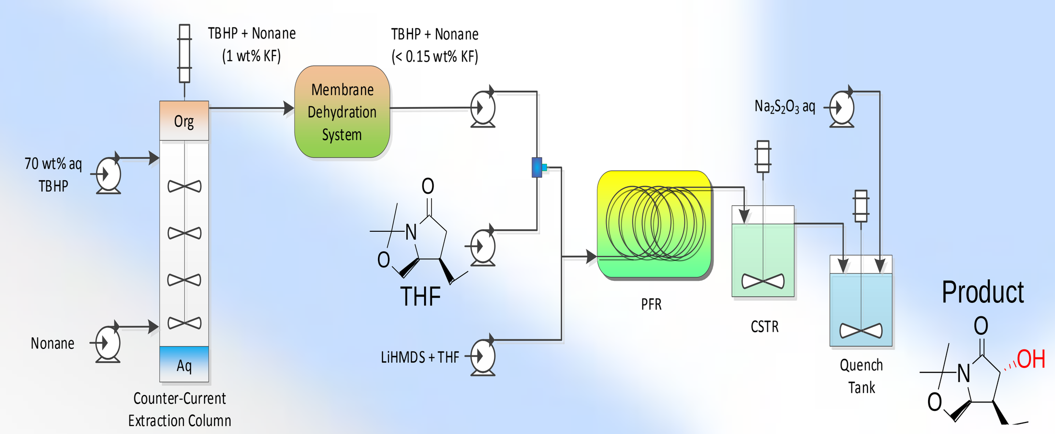
Streamlining Operational Units…
From 3 to 1 Continuous Stirred Tank Reactors (CSTRs)

Scale	Reactor Volume (L)	Residence Time (mins)	Material of Construction	Impeller Type
Campaign 1	24 (three 8L CSTRs)	40	316SS	Propeller
Campaign 2	50 (one 50L CSTR)	20	Glass	Propeller

- Oxidation reaction could be completed in a single CSTR with a reduced residence time of 20 mins.
- Similar mixing pattern achieved by keeping similar impeller and equivalent reactor geometry at different scales
- Larger CSTR combines the nominal working volume of the 3 smaller CSTRs and allows reaching steady-state dynamics faster

Full Integration of Operational Units up to Quench

Extraction >> Pervaporation >> Reaction >> Quench



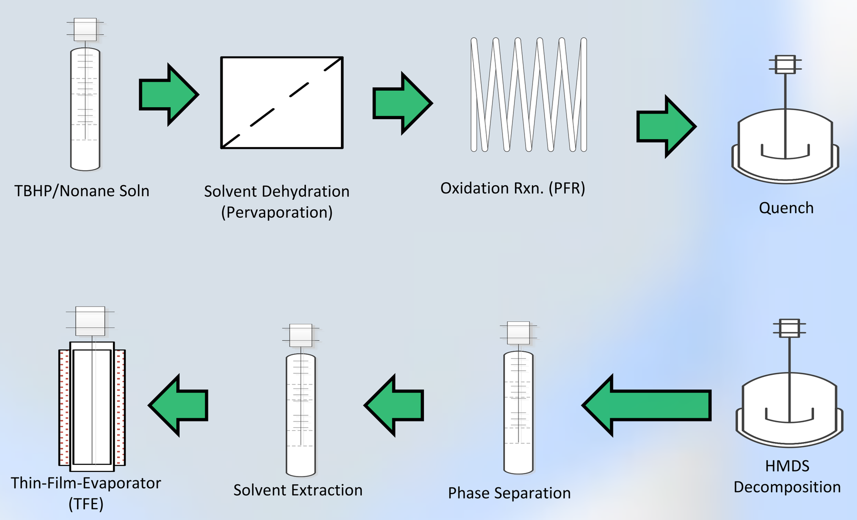
Campaigns Summary

Camp	Manufacturing Mode			Output of 8a		
	Extraction	Pervaporation	Reaction (Residence Time)	Potency-Corrected Weight (kg)	HPLC Purity (%)	Yield (%)
1	Batch	Flow	Flow PFR + 3 CSTR (115 mins)	**12.2**	80.4	72.6
2	Batch	Flow	Flow PFR + CSTR (90 mins)	**31**	80	71.8
3	Flow	Flow	Flow PFR + CSTR (90 mins)	**148.6**	84.2	75.9

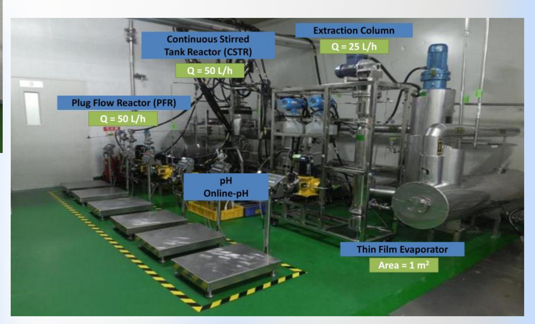
Process running continuously up to quench producing **192 kg** already… workup done in batch.

What else can be done to optimize and streamline this process?

End-to End…



4th Campaign: End-to-End Process (257 Kg Delivery)



Conclusions:

- 4 Production campaigns successfully completed (> 450kg delivered)
  - Yield 78~80%; Purity 99.8%
- Cycle Time Reduction (47 days to 19 days)
- Use of a powerful oxidizing agent in flow
- Design and Integration of a new operational unit (pervaporation) in the continuous manufacturing of an intermediate.
- Implementation of an end-to-end process
  - Competitive advantage over batch in terms of throughput, cycle time, and quality of product

Acknowledgments

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