DALHOUSIE UNIVERSITY
FACULTY OF ENGINEERING

Continuous Synthesis of Active Pharmaceutical Ingredients in a Reconfigurable, Miniscale Plant

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Introduction

- **Active pharmaceutical ingredients (APIs)** make up the bulk of the chemicals industry. Many APIs are outsourced internationally to reduce operational costs and availability of raw materials.
- **Continuous flow synthesis** provides the ability to produce APIs while reducing operation costs and promoting an inherently safer design. This concept is illustrated in **Figure 1**.

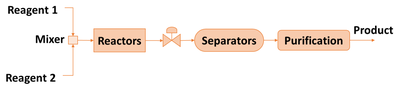

Figure 1. Continuous Flow Synthesis of APIs

- The goal of this project was to stimulate more Canadian independence with respect to pharmaceutical manufacturing.

Design Objectives

- **To design a modular, reconfigurable processing plant that produces APIs through a continuous process.**
- To meet the demand of a Phase III clinical trial by producing a minimum of 3000 doses per day.
- To produce APIs that meet Health Canada's Good Manufacturing guidelines.
- To ensure safe operation of miniscale plant.
- To produce APIs at competitive costs to current batch processes.
- To reduce the environmental impact of API production.

Design Process

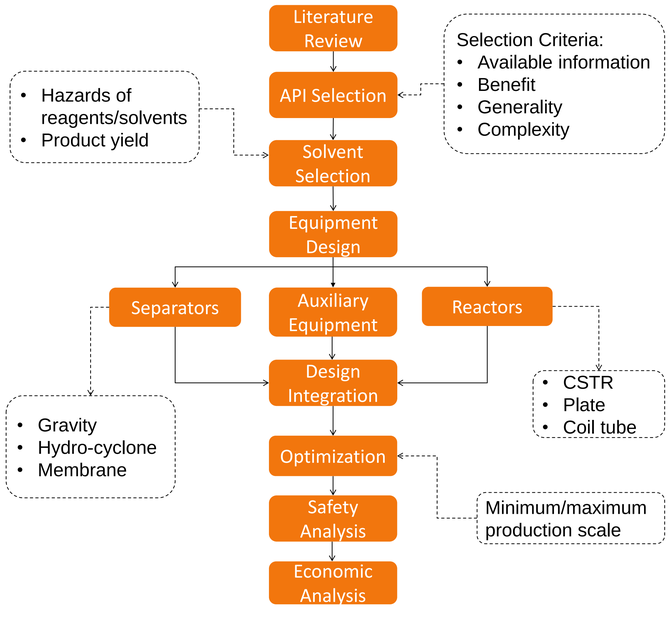

Figure 2. Flow chart of the design process.

Design Overview

Overall Process

- Miniscale plant designed through the **modeling of continuous flow syntheses of ibuprofen and diazepam.**
- Both process lines share a separator and supporting equipment, as can be seen in **Figure 3**.
- The design allows for units to be bypassed.
- Extensive pump design allows for higher API conversion and purity rates through intermediates.

Process Operation

- The **production range of diazepam** is 15–16.5 grams/day. This produces 3000-3300 doses/day.
- The **production range of ibuprofen** is 10.6 – 53.1 kg/day. This produces 53,000-266,000 doses/day.
- The range between the process lines allows for the choice of continuous flow synthesis with or without a solvent.
- Additional APIs including atropine, diphenhydramine hydrochloride, and lidocaine hydrochloride can be produced in this design.

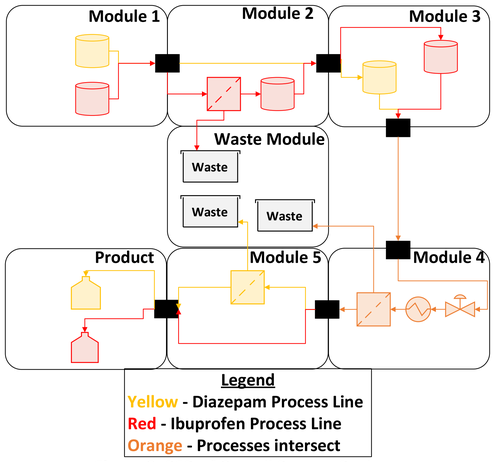

Figure 3. BFD of Overall Process Design

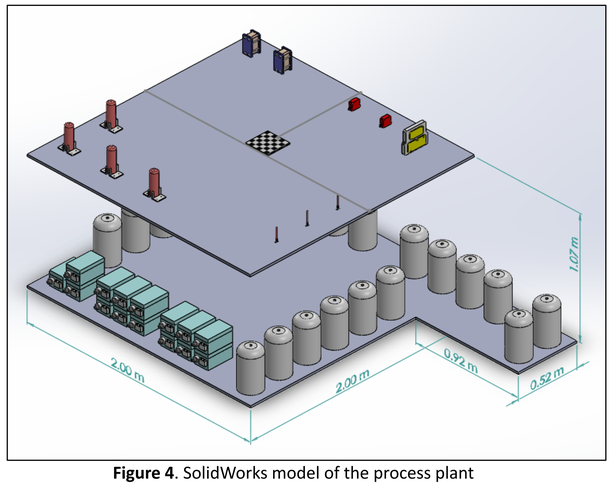

Figure 4. SolidWorks model of the process plant

Layout

- The dimensions of the plant can be seen in **Figure 4**. Process fits within a 50 ft^2 area (2 m x 2 m).
- Double layers were designed to minimize land use.
- Pumps and storage vessels on bottom layer. acids and bases separated.
- Reaction and separation units on upper layer. Area is available for expansion.
- PFA tubing used for process lines. Compatible with chemicals and operating conditions.

Safety Considerations

- Plant footprint minimized to allow operation within a walk-in fume hood.
- Minimized inventory of reagents.
- Provides safe relief venting throughout process design.
- Selected tubing and equipment compatible with chemicals and operating conditions.
- Solvents used were chosen based on Pfizer's selection guide for medicinal chemistry.

Separators

- **Separation units** are required to facilitate the removal of incompatible substances and waste from the product stream, and to prepare the intermediate product for further purification steps.
- The commercial membrane separator from Zaiput Technologies was selected for the separation units. The SEP-10 model is shown in **Figure 5**.

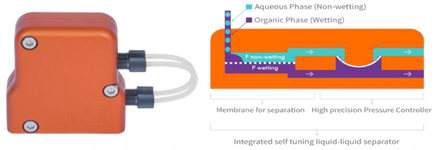

Figure 5. Zaiput inline liquid-liquid separator, model SEP-10 (left) and demonstration of operation (right) (Zaiput Flow Technologies, 2021).

- Separation is achieved based on differences in the interfacial tension between phases.

Reactors

- **Reactor units** are designed to convert the reactants in a continuous manner. Reactors chosen for the plant are shell and coil-reactors as seen in **Figure 6**.
- The dimensions of each reactor is custom-made to meet the demands of their respective reaction.

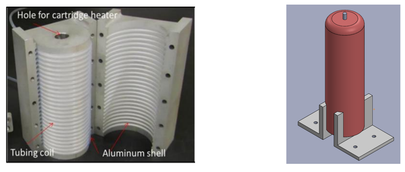

Figure 6. Close up of shell and coil reactor (left) and SolidWorks model of coil reactor (right) (Adamo et al., 2016).

- Average target residence time in these reactors is between 1 to 4 minutes. For longer residence times, reactor dimensions can be altered to meet the demand.

Economic Analysis

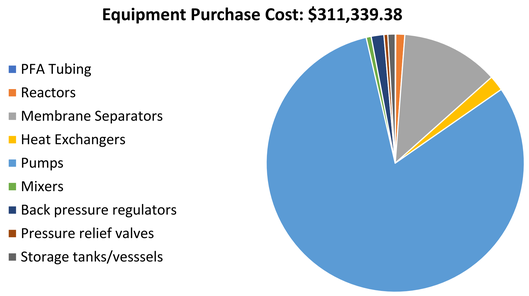

Figure 7. Equipment purchase cost.

- The pumps make up most of the equipment cost, which is typical for this type of processing plant due to the pressure and flow rate specifications. The cost of a HPLC and syringe pumps are $ 7,075 US and $ 20,400 US, respectively.

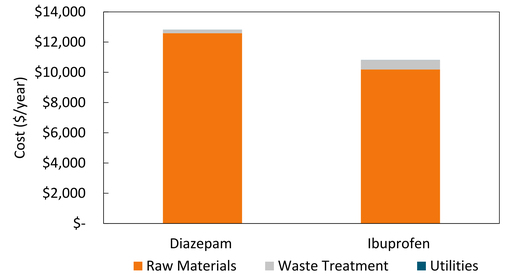

Figure 8. Annual operating cost

- The **operating cost** to produce the unpurified product is **$ 4693.39 US/kg of diazepam** and **$ 5.64 US/kg of ibuprofen**.

Conclusion

- The proposed continuous flow production plant consists of five reconfigurable modules, having five reaction units, three separation units, and 4 heat exchange units.
- Plant can accommodate API syntheses requiring intermediate separations and up to three reaction steps.
- The profitability of the processing plant is **dependent on the API being produced**. The continuous flow process may be more suitable for drugs with shorter lifespans and a low demand, such as orphan drugs.
- Further downstream processing units could be added to the system to allow purification steps to be performed in a continuous manner.

References

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