PURDUE UNIVERSITY

CAPSTONE EXPERIENCE 2014

Agricultural & Biological ENGINEERING

Targeted nano-chemotherapeutics for breast cancer treatment

Michelle Cox (BE), Curtis Morgan (BE), Stephanie Neace (BE), and Gordon Showalter (BE)

Objective: develop an industrial process for the manufacture of Nafaxane

Imparting directed targeting and enhanced bioavailability to anti-cancer drugs is a perpetual challenge of the pharmaceutical industry. Exploiting the advantageous physical properties of nano-scale materials and specificity of receptor-binding ligands, we have optimized both lab and industrial scale processes for the synthesis and manufacture of a unique nano-suspension of active pharmaceutical ingredient (API) co-crystallized with a receptor-binding coformer (CF) dubbed *Nafaxane*. These nano-cocrystals enhance directed targeting and bioavailability.

Background and Theory

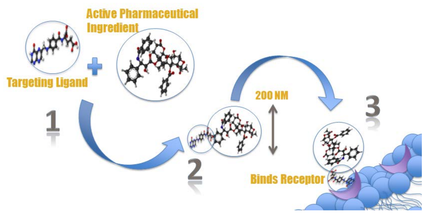


Figure 1: The biological background of Nafaxane

Advantages of nanoscale crystalline materials

- Collection in highly vascularized tissues due to Enhanced Permeation and Retention (EPR) effect[1]
- Increased solubility and bioavailability of hydrophobic materials[1]

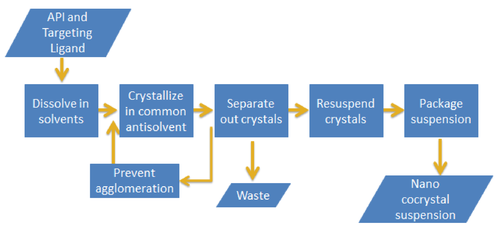
Advantages of receptor-specific ligands

- Directed targeting to specific tissues[2]
- Decreased side-effects compared to conventional chemotherapeutics

Experimental Design

- Framework established in previous literature[1] (Figure 2)
- Anti-solvent co-crystallization method
- Optimized with Paclitaxel as API
- Two factor full factorial

	API Concentration	Drug : Coformer
+	5 g/L	2:1
-	3 g/L	1:1



Anti-solvent Volume	Mixing Speed	Crystallization Time	Temp	Sonication	Solvent Volume
20 mL	1000 RPM	10 min	0 C	Yes	1 mL

Figure 2: Process flow and parameters of nano co-crystallization (ABOVE)

Results

TEM images (Figure 3) was used to confirm size of the crystals, which are nano in width, although micro-scale in length. Differential Scanning Calorimetry (DSC) was used to confirm crystals formation by comparing profiles for paclitaxel alone, ligand alone, and crystals. Data was inconclusive for the first round and additional characterization is required.

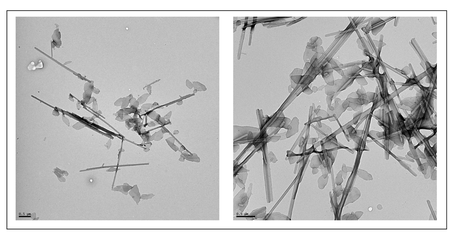


Figure 3: TEM images of product solutions show both nano and micron sized crystals. The size bar is 0.5 um

Final Design

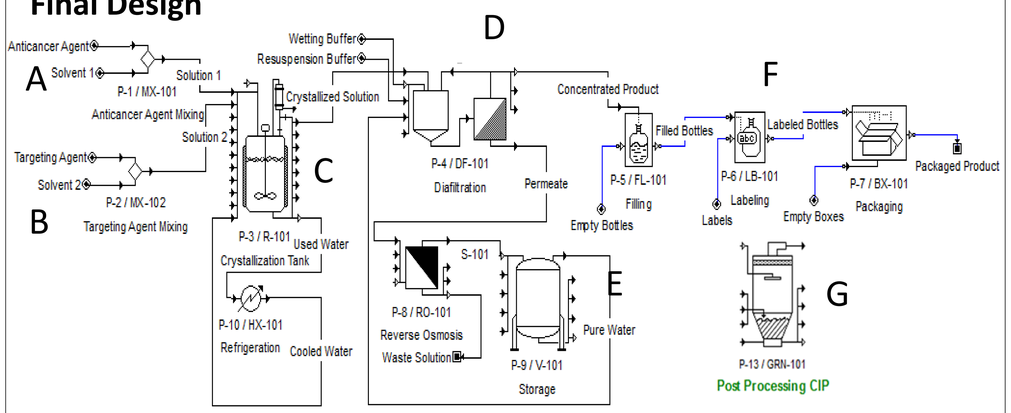
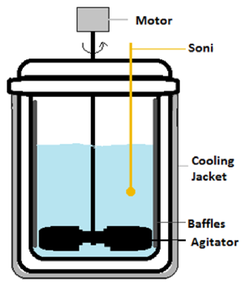


Figure 4: Industrial Process Flow for nano co-crystal production

Unit Operations

Scale up values for the final industrial scale process (Figure 4) were calculated from production volumes based on market shares of our main competitor, *Abraxane*. The annual production volume is 288 L of product for a market of 128,000 patients by 2019.



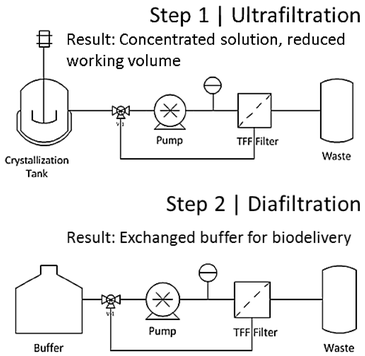


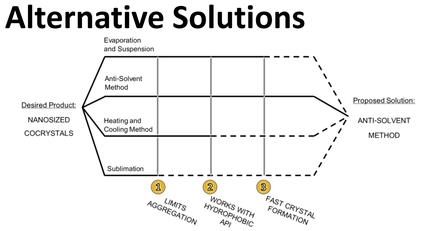
Figure 5: Detail of unit operations for crystallization tank (LEFT) and filtration (RIGHT)

Safety and Sustainability

- Caustic clean-in-place materials present safety hazard (NaOH and H_3PO_4)[3] (**G**)
- Required off-site processing of any API or Coformer waste
- Water from diafiltration is purified by reverse osmosis and recycled (**E**)
- Refrigeration unit recycles water
- Potential environmental impact on Yew Tree due to increase taxol demand
- Quality-assurance sampling along process (**A, B, C, D**)

Figure 6: The Pacific Yew Tree is the source of taxol

Alternative Solutions



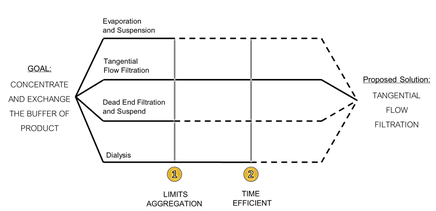


Figure 7: Morphological charts comparing alternative solutions for crystallization (LEFT) and filtration (RIGHT)

Economics[4]

- **Equipment Cost**: $24,101
- **Annual material cost:** $613,234
- **Desired ROI**: 50%
- **Calculated Unit Cost**: $782
- **Time of Return**: 1.54 years

Equipment Costs

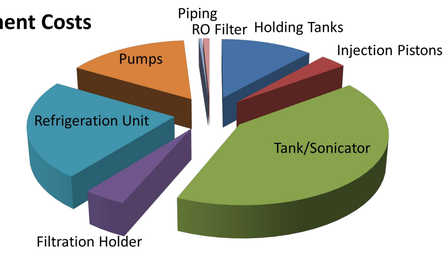


Figure 8: Elements of equipment purchasing costs (ABOVE) and material costs (BELOW)

Material	Cost	% Cost
PXL	$112,400.00	18.32904
CF	$854.49	0.139341
DMSO	$34,580.00	5.638952
NaOH	$7,770.00	1.267052
H_3PO_4	$7,630.00	1.244222
Filter	$450,000.00	73.38139
Total	$613,234.49	100

Material prices from Sigma Aldrich and Fischer Scientific

Impact: How does Nafaxane Compare?

	Abraxane	Nafaxane
Method of Action	Albumin-Bound	Ligand co-crystallized
Cost per Unit	$4200[5]	$782
Potential Side Effects	Nausea, vomiting, diarrhea, mouth sores, headaches, muscle and joint paint, neuropathy, diziness[6]	Risk of infection*, bruising and bleeding*, anemia*, diarrhea*, sore mouth*, fatigue*, hair loss*[3]. Kidney damage**
Method of Delivery	Injectable	Injectable
Potential Use	Breast, lung, pancreatic, and non-small cell lung cancers	Breast, ovarian, colon, renal, and lung cancers, mesothelioma, myeloid leukemia, neck carcinomas, and pediatric ependymal brain tumors

*From generic paclitaxel only (un-bound)
**From directed targeting

References

1. Li, T. (2006). *US Patent No.* 20060280680A1. Washington, DC: US Patent and Trademark Office
2. Peer, D., Karp, J., Hong, S., Farokhzad, O., Margalit, R., & Langer, R. (2007). Nanocarriers as an emerging platform for cancer therapy. *Nature Nanotechnology* 2, 751-760.
3. MSDS Search and Product Safety Center. (2014). Sigma Aldrich. Retrieved from sigmaaldrich.com/safety-center.html
4. Peters, M., Timmerhaus, K., and West, R. (2002). *Plant Design and Economics for Chemical Engineers*. McGraw-Hill. New York, NY 2002.
5. Berenson, A. (2006). Hope at $42000 a Dose. *New York Times*, October 1 2006. Online edition.
6. Abraxane. (2013). Celgene Corporation. Retrieved from www.abraxane.com

Acknowledgements:

Sponsor: J. Irudayaraj, Ph.D.

Course Instructor: M. Okos, Ph.D.

Technical Mentor: P. Bhandari, M.S.

PURDUE AGRICULTURE
PURDUE UNIVERSITY

PURDUE ENGINEERING
Think impact.