DeSouza Process - Pregabalin: Transformed Crystallization

A partnership between **Pfizer** (Ringaskiddy, Cork, ***Ireland***) and SSPC, the SFI Research Centre at the **University of Limerick (UL).**

The Challenge:
In 2012, Dr {atrick Frawley started taking Lyrica (Pregabalin) for severe nerve pain associated with his spine. He decided to use his expertise in predictive modelling, process design and fluid mechanics to reduce the cost of manufacture. The strong working relationship between Dr Patrick Frawley, (UL) & Pfizer facilitated easy interaction and a SFI TIDA programme application was assembled. Two postdocs in UL worked with the Pfizer team in the Process Development Centre Cork, who shared manufacturing procedures and materials. The problem statement was clear and related to process inefficiency, complexity and cost.

Project Impact:
The research has significantly impacted a manufacturing process within the pharmaceutical sector. This is evident through an increase in yield, improved efficiencies, and reduction in solvent use and complexity, improvements in throughput and better particle consistency. The candidate API selected for optimisation, Pregabalin known by the brand name Lyrica, was and remains one of Pfizer's biggest multi-billion euro selling APIs. Significant economic benefits will be derived from this research. This work has also built bridges and credibility between Irish plants and US corporate units through active engagement, regular meetings with Research Laboratories in the US and the exchange of key staff. Publication: Solubility of (S)-3-(Aminomethyl)-5-Methylhexanoic Acid in Pure and Binary Solvent Mixtures, J. Chem. Eng. Data, DOI: 10.1021/acs.jced.5b00736.

Project Solution:
The finalised innovative solution developed was divided into two parts.

The first part of the solution involved changing from a complex four step crystallization procedure using a modified solvent matrix to a single cool down procedure. This provided considerable benefits, in terms of time, throughput, solvent costs and Particle Size Distribution. Despite the many benefits of this approach, application of this step alone had been calculated to result in a similar yield to the current crystallisation procedure at plant scale - hence the requirement for a further step.

The second part of the solution focused on maximising yield. It is critical to maximise yield as API which is not returned from the solution represents a loss, and this can be a significant expense for the pharmaceutical manufacturer. This was realised by pressure recrystallization thus increasing the solvent boiling point and allowing for a higher solubility at the process start. It is important to note that the improvements described could be applied either individually or synergistically in combination. A lack of uniformity in particle size distribution can have consequences for downstream processes such as filtering and drying. The pressurisation approach has the advantage of preserving the benefit of a monomodal PSD. Pressure recrystallisation, as a means of improving yield, has been championed in the University of Limerick using several commercially available API's including paracetamol. A novel test rig, developed in the University, allows for non-intrusive high temperature / high pressure measurements, which could not be obtained using the standard gravimetric approach. This platform technology is being developed further with potential commercialisation in the future. This approach is been considered for other processes being redesigned by the PDC at Pfizer.

"An application that has significantly impacted a manufacturing process within the pharmaceutical sector".

Prof Liam Tully, Pfizer Global Process Development Centre.