INVESTIGATING THE ISOLATION PERFORMANCE OF A NOVEL CONTINUOUS FILTRATION UNIT FOR PHARMACEUTICAL PROCESS DEVELOPMENT AND MANUFACTURING: A CASE STUDY USING PARACETAMOL AND RELATED IMPURITIES

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There is a significant gap in the availability of equipment with appropriate capacity for laboratory process development, pilot plant and small manufacturing scale using dead end continuous filtration and drying. To advance small-scale pharmaceutical isolation forward from traditional batch Nutsche filtration to continuous processing, a continuous filter dryer prototype unit (CFD20) was developed in collaboration with Alconbury Weston Ltd (AWL) as part of the REMEDIES program. The technical challenges and the key performance indicators for such a unit were identified and the prototype solution was evaluated by comparing the functionality and performance of the CFD20 unit against manual best practice executed using a Biotage manual filtration unit. Two different paracetamol grades, micronized and granular, were selected as model materials and Patent V blue dye as a soluble impurity. The knowledge gathered during this work was used to facilitate the development of a commercial unit (CFD25).

In order to test the utility of the CFD25 as a process development tool a design of experiment approach was used to develop a procedure to reduce agglomeration during isolation and to enhance impurity removal. The effect of input slurry properties, such as solid loading, particle size distribution and crystallization solvent were investigated to determine their impact on the filtration and washing performance and the characteristics of the dried product. Two different grades of API were used, typical crystalline product and micronized. The role of washing was explored by analyzing the effect of different crystallization and wash solvents and the amount of wash solvent used to remove paracetamol related impurities such as acetanilide and metacetamol. Product crystal suspensions were prepared using three potential crystallization solvents; ethanol, isopropanol and isoamyl alcohol. Three different wash solvents were selected; n-heptane and isopropyl acetate were selected based on their miscibility with the primary crystallization solvents to facilitate diffusional and dilution washing mechanisms; isopropyl acetate and n-heptane exhibit relatively high and very low paracetamol solubility respectively. The third solvent n-dodecane was selected as an immiscible wash solvent to illustrate displacement washing. In each case, the wash strategy was design to minimize the nucleation of new crystals during washing.

Filtration cake properties were determined using the inbuilt machine vision system which was used to halt filtration at dryland and to record filtration data. The filter cake and filtrate were both analyzed to quantify the purity achieved using HPLC. The isolated product was also analyzed to evaluate mechanical properties; the extent of agglomeration, the agglomerate particle size distribution and the agglomerate strength. Proton nuclear magnetic spectroscopy was used to determine the residual solvent in the dried filter cake. The AWL CFD25 is a versatile unit capable of reducing the time to isolate and dry API compounds and it is able to process modest quantity of slurry per cycle allowing experimental design to be conducted. A good level of purification was

achieved using wash volume equivalent to 4 cake void volumes. It was demonstrated that low boiling aliphatic hydrocarbons are particularly effective to reduce the extent of agglomeration and to form softer agglomerates.