Flowsheet model: filtration and washing parameters estimation and strategies implementation.

Linking first crystallization through first isolation

- The pharmaceutical industry is starting to adopt continuous active pharmaceutical ingredient (API) manufacturing;
- To facilitate the complete transition from batch to continuous manufacturing it is necessary to “smartly” integrate single continuous unit operations to achieve a continuous material flow from synthesis to formulation;
- Digital design of continuous API manufacturing offers a path to achieving this goal.

1 From batch-wise lab scale experiments…

Filtration → Wash 1 → Wash 2, 3 → Dissolution

…continuous isolation strategy can be designed by a prediction first approach.

2 Using parameter estimation…

- Correlation porosity and driving force
- Heel effect

3 …and global sensitivity analysis…

- Solid content vs filtration properties
- Particle size distribution effect on filtration and washing properties
- Diffusion coefficient on impurity removal
- Porosity and wash ratio during washing
- Particle sphericity impact on washing

4 …the isolation strategy is designed.

Critical Material Attributes
- Crystallisation CQAs:
  - PSD
  - Initial slurry composition
  - Morphology

Critical Process Parameters
- Driving force (400 bar)
- Wash solvent (n-heptane)
- Number and volume of washes (3 ECV)

Critical Quality Attributes
- Purity
- Residual mother liquor content

Conclusions

- A filtration and washing model has been developed to predict the first isolation of metomenamic acid campaign
- The model has useful predictive capabilities shown to match outcomes determined experimentally by DoE
- A global sensitivity analysis reveals how the variance of the model output depends on the uncertainty of the input factors
- The flowsheet model enables unit operation strategy design from a limited amount of experiments, allowing prediction of integrated unit system performance

References: