Process development for recovery of crystals using DoE

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Abstract

- Early process design of a dead end filtration operation for the recovery of crystals of active pharmaceutical ingredients relies on small-scale data acquired with just a few mL of particle suspension using a filter with a diameter of a few mm.
- For rapid process development it is important **to gain early information on** the filterability of the process stream regarding flux rate and cake compaction under different process conditions such as pressure difference (ΔP), and filter pore size as a function of particle size distribution (PSD) and crystal concentration.
- The effect of these process variables is investigated on process performance. A **design of experiment (DoE) tool** was also employed to fit the experimental data.
- In this work, a case study is presented on the characterisation of an **active pharmaceutical ingredient (API)** - acetaminophen using laser diffraction and microscopic imaging techniques. The effect of changes in process parameters including pressure difference, PSD and concentration on filterability were investigated experimentally.
- The filtration rate was investigated at pressure driving forces of 100 to 700 mbar and for mean particle sizes d(50) ranging from 40 to 320 µm. The experimental design allowed the utilisation of filter capacity to be optimised and also enables predictive assessment of other process conditions.
- Parity plots show good data fitting was possible across the range of variables studied.
- The findings could further enhance a better understanding of the recovery filtration operations at laboratory scale.

Aim and Objectives

Aim

Biotage VacMaster (BVM) filtration systems are used at millilitre scale both **to mimic full-scale processing operations and to gain understanding of the effect of the engineering environment** on the properties of the material being processed.

Objectives

- Evaluation of the use of BVM system for the study of crystal recovery
- Characterise the active pharmaceutical ingredients
- Implement quality by design approach using MODDE for -
  - Experimental design
  - Screening of variable of importance
- Understand the response of crystals to process conditions such as ΔP
- Develop a predictive model using MODDE
- Validate the model for prediction of process conditions

Filtration Flux Determination

1. Record filtrate volume V, recovered versus time t at fixed ΔP
2. Explore the effect of process variables on crystal size, filter pore size 5 µm on the resultant average flux rate.

Process Flow Diagram

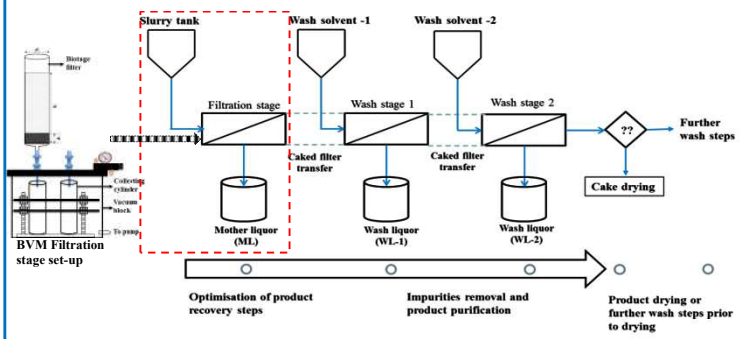


Figure 1: Process flow diagram showing a recovery filtration step followed by two wash stages. This presentation focuses on the product recovery step only.

Characterisation of API

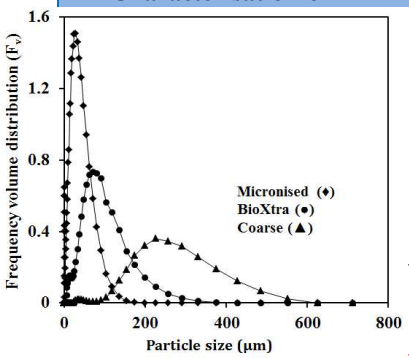
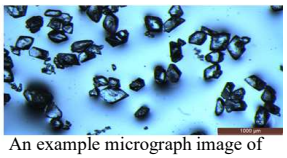


Figure 2: Particle size distribution (PSD) of acetaminophen crystal size bands. The micronised sample shows some significant amount of fines.



An example micrograph image of coarse acetaminophen showing the prevalent orthorhombic shape of the acetaminophen.

✓ The PSD plot shows a normalised logarithmic - percentage volume distribution to frequency volume distribution.

✓ For the normalisation, the volume fraction of particles in size range d_1 to d_2 is given by $\int_{d_2}^{d_1} F_{v,i}\mathbf{d}d \Big/ \int_0^{\infty} F_v \mathbf{d}d$.

(Chatel et al., 2014)

Results

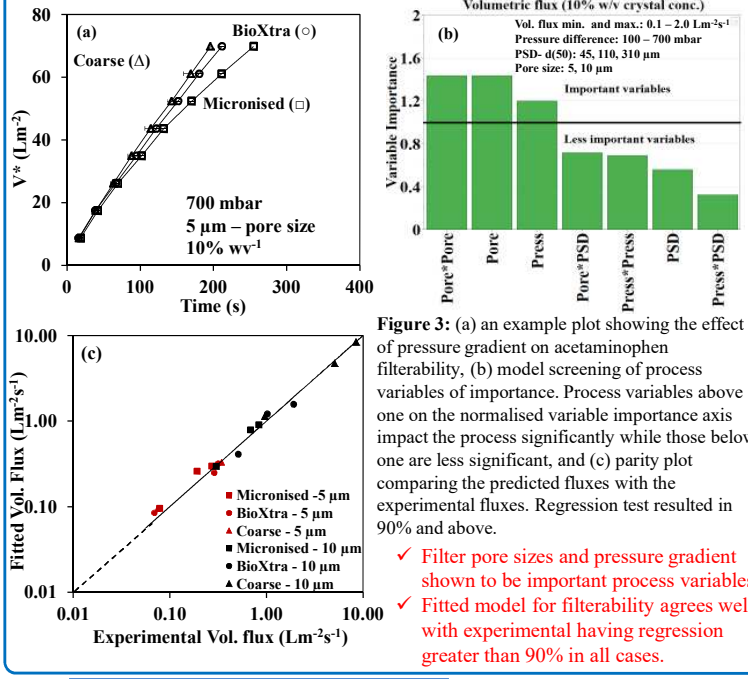


Figure 3: (a) an example plot showing the effect of pressure gradient on acetaminophen filterability, (b) model screening of process variables of importance. Process variables above one on the normalised variable importance axis impact the process significantly while those below one are less significant, and (c) parity plot comparing the predicted fluxes with the experimental fluxes. Regression test resulted in 90% and above.

✓ Filter pore sizes and pressure gradient shown to be important process variables.

✓ Fitted model for filterability agrees well with experimental having regression greater than 90% in all cases.

Conclusions

- The application of Biotage VacMaster to study the effect of filtration process conditions on crystal's isolation based on sizes has been demonstrated.
- Implementation of **QbD for early understanding of process variability** has been established.

Acknowledgments

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References: Chatel, et al, (2014). Biotechnology and Bioengineering, 111(5), 913–924.