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-08-52

Quality by design approach for early understanding of active pharmaceutical ingredient recovery process through dead-end filtration

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PURPOSE

This study applied **some concepts of quality by design (QbD)** to crystal recovery through filtration. A bespoke laboratory scale dead-end filtration platform (modified Biotage vacuum master (BVM)) was used to investigate the recovery of an active pharmaceutical ingredient (API) of different size distributions using acetaminophen crystals (micronised, medium-sized Bioxtra and coarse) as a case study.

The approach involved:

(1) identification of critical process parameters (CPPs) with significant impact on process stability (a process risk evaluation step based on one-factor-at-a time);

(2) design of experiment to screen the influence of design factors (such as filter pore size, pressure difference, crystal loading and particle size distribution (PSD)) contributing to process instability based on process responses (volumetric flux and specific cake resistance); and

(3) investigate the optimal process window for reduced probability of failure and process predictability.

OBJECTIVE

- The primary goal of this work is to investigate the use of DoE approaches as an element of QbD for early process understanding coupled with the development of a predictive model for the filtration of acetaminophen as a representative API.

METHOD(S)

- The experimental plan was developed using DoE, and the experimental data generated was analysed using partial least square (PLS) method to determine the relative importance of different factors.

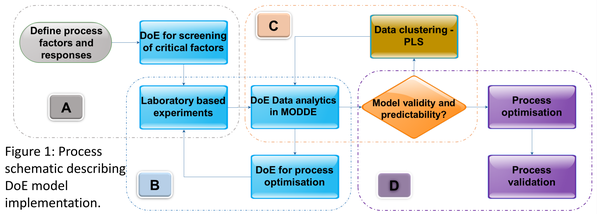

Figure 1: Process schematic describing DoE model implementation.

Process factors

Name	Units	Settings
Press diff	mbar	100 to 700
Particle size	µm	45, 110, 310
Crystal conc	% w v^{-1}	10 to 30

Process responses

Name	Units	Min.	Max.
Vol flux	L m^{-2} s^{-1}	0.2	2.0
Spec cake resis	M kg^{-1}	11.5	20400.0

A. Definition of process factors and responses based on one-factor-at-a-time rapid experimental evaluation of the process followed by DoE design and experimentation. **Two conditions investigated**.

B. Initial data analytics based on inbuilt statistical models to identify critical process factors followed by DoE design for process optimisation, lab experimentation and data analytics.

C. OPLS Data clustering and reprocessing excluding outliers and reprocessing in MODDE. Confirm model validity and progress to

D. Process optimisation by setting boundary conditions and validating predicted process responses.

RESULT(S)

A

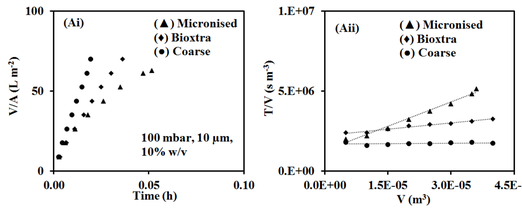

Figure 2: An example volumetric flux profiles (i) and Darcy plots (ii) for acetaminophen crystal size bounds at 10% wv^{-1} crystal load filtered at conditions of 100 mbar.

	Volumetric flux (L m^{-2} h^{-1})		Specific cake resistance (m kg^{-1})	
	Condition 1	Condition 2	Condition 1	Condition 2
Data-Model fitness (R^2)	0.8992	0.9037	0.8703	0.9697
Reproducibility	0.9970	0.9998	0.9971	0.9965

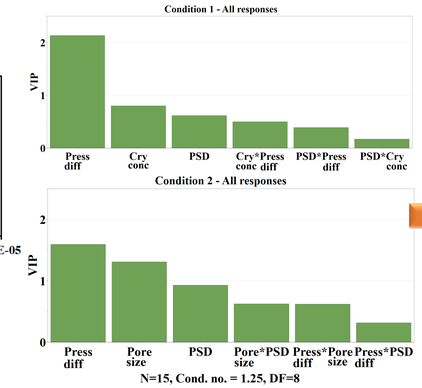

Figure 3: VIP showing importance of each process variables to process responses based on the screening experiments (refer to Table 1 and 2). (A) and (B) are for Conditions 1 and 2 respectively. **Bars above 1 indicate variable of importance having significant effect on the process.**

B

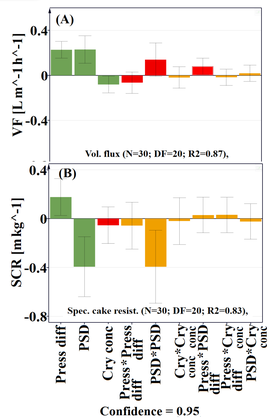

Figure 4: Verification of model suitability for understanding process factors interaction for (A) volumetric flux (VF) and (B) specific cake resistance (SCR) scaled and centred regression coefficients.

Table 2: Summary of fit and VIP data summarised. Colour coding refers to Figure 4.

Conditions		R^2	Q^2	MV	Rep.	VIP: PSD	Pres diff	Cry conc	PSD* PSD
Unrefined fit (■■■)	VF	0.87	0.68	-0.20	0.99	2.18	1.35	NS	1.67
	SCR	0.83	0.67	-0.20	0.99				
Refined fit (■■)	VF	0.97	0.59	0.29	0.99	1.67	1.09	0.40	1.24
	SCR	0.93	0.89	0.23	0.99	1.65	0.51	0.15	NA
Auto-tuned fit (■)	VF	0.90	0.86	-0.18	0.99	1.46	0.88	0.32	NA
	SCR	0.92	0.90	0.22	0.99	1.35	0.42	NA	NA
Post-SIMCA	VF	0.98	0.84	0.52	0.99	1.66	1.48	1.05	NA
	SCR	0.98	0.88	0.90	0.99	1.57	1.32	NA	1.12

VF – volumetric flux, SCR – specific cake resistance, MV – model validity, PSD – particle size distribution, Pres diff – pressure difference, Cry conc – percentage crystal loading, Rep – reproducibility, R^2 – data-model fitness, Q^2 – model predictability .

- **Three stages model refinement to achieve a model with good reproducibility and predictability.**

D

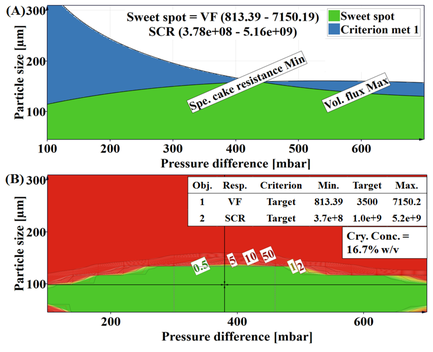

Figure 8: 2D diagrams showing the interactions between factors and responses. Figures represent (A) sweet plot, and (B) probability failure plot.

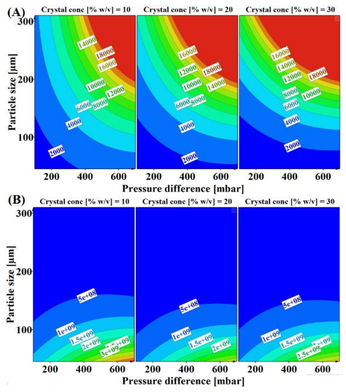

Figure 7: 4D surface response diagrams showing the interactions between factors and responses. Figures represent (A) volumetric flux, and (B) specific cake resistance.

C

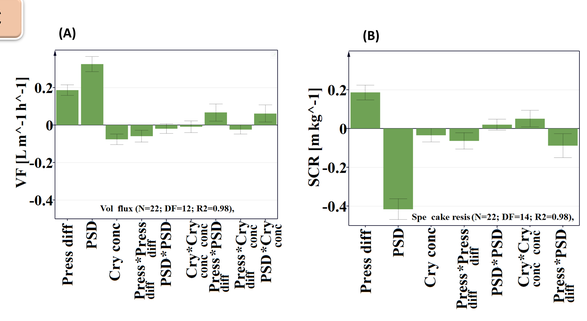

Figure 6: Model verification based on coefficient or regression to understand process factors interaction and predictability of process responses for (A) volumetric flux, and (B) specific cake resistance. Some experimental data points were excluded for modelling purposes.

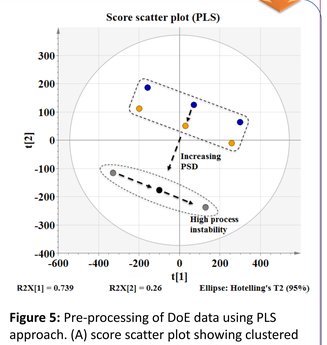

Figure 5: Pre-processing of DoE data using PLS approach. (A) score scatter plot showing clustered data based on PLS model and The blue coloured dots and bar charts represent condition of high probability of experimental failure considered for exclusion in the DoE. The yellow, grey and blue colours represent the micronised, Bioxtra and coarse respectively.

CONCLUSION(S)

- Process predictability was demonstrated by data clustering and refinement based on partial least square model.
- The results showed good predictability with >98% regression between the predicted and experimental data.
- Verification of optimal operating window with less than 5% probability failure resulted in conditions of 300 – 450 mbar pressure difference and PSD of 45 – 110 µm.
- The approach studied using the small-scale BVM provided an early data gathering and systematic approach to understanding process interactions affecting crystal recovery through dead-end filtration.

FUNDING / GRANTS

This work was supported/funded by EPSRC UK through Centre for Innovative Manufacturing, UCL in collaboration with EPSRC Centre for Continuous Manufacturing and Crystallisation (CMAC), University of Strathclyde. Also, our appreciation goes to Sara Ottoboni and Thomas McGlone for supporting on experimental set-up and Pol MacFhionnghaile, Ian Houson, Nazer Rajoub for advising with setting up of DoE tools.

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