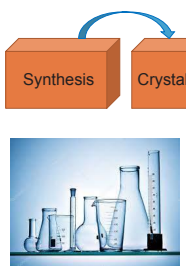
POSTER 11

Integrated Filtration and Washing modelling: Optimization of Impurity Rejection for the Filtration and Washing of Active Pharmaceutical Ingredients

Sara Ottoboni[1,2*], Bhavik Mehta[1,3], Ekaterina Gramadnikova[1], Cameron J. Brown[1], Niall A. Mitchell[3]

[1]EPSRC Future CMAC Manufacturing Hub University of Strathclyde, Glasgow, UK
[2]Department of Chemical and Process Engineering University of Strathclyde, Glasgow, UK
[3]Siemens Process Systems Engineering Ltd., London, UK

Context: Transitioning pharmaceutical manufacturing from batch to continuous provides opportunity to improve sustainability.



Digital design of continuous API manufacturing offers a path to reduce the quantity of material consumed during process development

Aim: Develop an integrated mechanistic filtration and washing model and accompanying optimization workflow to minimize impurities in the isolated filter cake.

Materials and methods

PE = experiments used for parameter estimation
V = experiments used for model validation
• = experiment replicas

Related impurities: 2-chlorobenzoic acid 2-3-dimethyl-N-phenylaniline Benzoic acid Copper (II) acetate
Filtration: 50mL dose stopped to dryland

Expt ID	PE or V	Crystallization Solvent	Wash Solvent	Isolation Pressure (mbar)	Wash Solvent cake volume	Number of Washes
1	PE	Ethyl Acetate	Cyclohexane	100	2	3
2	PE	Diglyme-Water	Heptane	600	2	3
3	PE	Ethyl Acetate	Heptane	600	2	2
4	PE	Ethyl Acetate	Heptane	100	4	2
5	V	Diglyme-Water	Cyclohexane	100	4	2
6*	PE	Diglyme-Water	Cyclohexane	350	3	3
7*	V	Diglyme-Water	Cyclohexane	350	3	3
8	V	Diglyme-Water	Heptane	100	4	3
9*	V	Diglyme-Water	Cyclohexane	350	3	3

Equipment/simulation tools	Purpose
Biotage VacMaster	Manual filtration and washing unit
Mastersizer 3000 laser diffraction	Particle size analyzer of the feed and isolated solid
HPLC	- Composition of filtrate removed during filtration and washing stages - Solid composition of the isolated cake
COSMO*Therm*	Solubility simulation
gPROMS FormulatedProducts	Filtration and washing process modelling

Model development

1. Filtration model (batch pressure filter) — -Carman – Kozeny equation(1) to simulate cake resistance; -Darcy's law(2) filtration to simulate filtrate flow rate; -Filtration stopped at dryland
2. Integrated filtration and washing model (continuous pressure filter) — - Filtration simulated as in stage 1, integrated with washing; - Washing modelled with displacement mechanism; -No changes in solid phase are considered (no particle dissolution or growth)
3. Washing model (MSMPR crystallizer) — -Filtration model (stage 1) outcome to feed washing model; -Washing modelled with diffusion – dispersion mechanism(3); -No particle dissolution or growth

Filtration:

$$\alpha_{av} = \frac{180\,(1-\varepsilon)}{\rho_s x_{sv}^2 \varepsilon^3} \qquad \frac{dV}{dt} = \frac{A^2\,\Delta P}{\mu\,(\alpha_{av} c V + A R_m)}$$

Washing:

$$W_r = \frac{V_w}{V_p} = \frac{u_s t}{L \varepsilon_{av}}$$

Displacement washing:

$$c_{j,e} = \begin{cases} c_{j,i} & if W_r < 1 \\ c_{j,w} & if W_r \geq 1 \end{cases}$$

Diffusion dispersion washing:

$$D_L \frac{d^2c}{dx^2} - \frac{u_s}{\varepsilon_{av}} \frac{dc}{dx} = \frac{dc}{dt}$$

Factor	Definition	Unit	Factor	Definition	Unit
ε	Cake porosity	-	c	Dry cake mass per unit volume of filtrate	kg m^{-3}
V_s	Volume of solids	m^3	V	Filtrate volume removed	m^3
V_{cake}	Total volume of cake	m^3	W_r	Wash ratio	m^3 m^{-3}
α_{av}	Average specific cake resistance	m kg^{-1}	V_w	Volume of wash	m^3
ρ_s	Density of solids	kg m^{-3}	V_v	Volume of voids	m^3
x_{sv}	Volume equivalent diameter	m	u_s	Superficial velocity of wash	m s^{-1}
t	Time	s	L	Cake height	m
A	Filter area	m^2	$c_{j,i}$ / $c_{j,e}$	Solute concentration initial, at the exit of the filter cake	-
ΔP	Pressure drop along the filter axis	kg m^{-1}s^{-2}	$c_{j,w}$	Inlet wash solvent concentration	-
μ	Filtrate viscosity	kg m^{-1}s^{-1}	D_L	Axial dispersion coefficient	m^2 s^{-1}

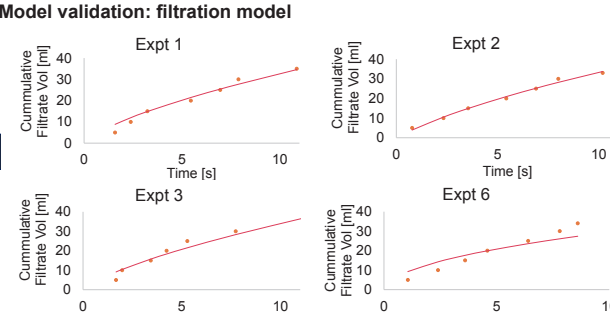
Results

Parameter estimation

Crystallization Solvent	Wash Solvent	Cake Porosity (empirical value 0.44)	Simulated Medium Resistance (1/m)	Compressibility Index, n
Diglyme-water	Heptane	0.694	1.31x10^8	0.833
Diglyme-water	Cyclohexane	0.5258	1.31x10^7	0
Ethyl acetate	Heptane	0.4804	1.6x10^9	1.312
Ethyl acetate	Cyclohexane	0.476	1.46x10^9	0

- Pharmaceutical cakes are generally low-moderately compressible (n<1). (4)
- Cake and filtration estimated parameters show good fit with the porosity.
- Cyclohexane cases show n=0 due to not enough data for PE.

Model validation: filtration model



- Simulated Darcy's plots accurate in reproducing the experimental filtration flow rate evolution.
- Less accuracy for experiment 6: errors in manually collecting the experimental data.

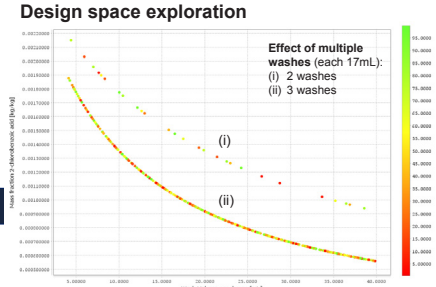
Model validation: washing models (Exp 3)

Solvent mass left filtration (kg)	Solvent mass left wash 1 (kg)	MFA concentration wash 1 (kg/kg)	CBA concentration wash 1 (kg/kg)
Experimental data			
3.73E-03	9.56E-04	1.21E-03	2.48E-03
Displacement model			
2.06E-03	1.63E-03	1.47E-04	1.33E-04
Diffusion dispersion model			
N/A	4.65E-04	1.11E-03	1.00E-03

WASHING DISPLACEMENT MODEL:
- Accurate filtration end point simulated.
- Not able to predict the liquid composition due to lack of diffusion dilution mechanisms.

WASHING DIFFUSION DISPERSION MODEL:
- Better accuracy in simulating the concentration of solute species removed during washing.
- Not able to predict residual solvent mass due to semi-batch operation and holdup specifications used.

Design space exploration



- The more wash solvent you use, the better is the purity achieved.
- No meaningful impurity improvement with >20mL (3 equivalent cake volumes) of wash solvent used.
- Multiple washes do have an effect on the impurity concentration.

Summary & Conclusions

- Developed a mechanistic model-based workflow for the optimization of an integrated filtration and washing model.
- Good match achieved between the estimated and experimental cake and filtration parameters.
- The pressure filter model is not able to predict the composition of filtrate removed well enough due to the displacement washing mechanism; better prediction achieved with diffusion-dispersion mechanisms, so diffusion-dispersion model used for design space exploration to identify which washing conditions reduce the final cake impurity concentration.
- Strong correlation between wash solvent volume used and number of washes and purity achieved.

References

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