WFC13: Solid/Liquid Separation track, L3.5, Paper 3001066

IMPURITY REMOVAL DURING FILTRATION AND WASHING – A MECHANISTIC MODELLING APPROACH

Mehta, B. A.[1,2], Ottoboni, S.[2,3], Gramadnikova, E.[2], Brown, C. J.[2], Mitchell, N. A.[1]

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

*Corresponding Author: bhavik.mehta@strath.ac.uk

Proceeding for the WFC13, Oct 6-9, 2022, San Diego, CA, USA

KEYWORDS: Filtration, washing, process modelling, optimization, impurity rejection

ABSTRACT

The focus of the work reported here combines filtration and washing operations commonly used in active pharmaceutical ingredient (API) purification and isolation by combining predicted and experimental data generated during upstream crystallization process. In detail, this work focuses on the development of a mechanistic model-based workflow for the optimization of an integrated filtration and washing model, with a view to minimize impurities in the isolated cake.

A Carman-Kozeny filtration model is integrated with a custom diffusion with an axial dispersion washing modelling approach. The custom washing model describes a washing process where the feed wet packed bed obtained by filtering a suspension to dryland is washed by diffusion-dispersion mechanisms. To effectively track impurities in the cake, the diffusion-dispersion wash model considers dissolution of the solid phase. The model was designed as a series of 10 continuous stirred-tank reactors (CSTR) where the approach used to mimic the dispersion washing mechanism modelled with the plug flow (PF) approach. The integrated modelling tool uses information on the product crystal suspension characteristics predicted using gPROMS FormulatedProducts to predict filtration time, filtrate flow rate, and the composition of the filter cake and filtrate generated during filtration. The washing of the wet filtered cake is then simulated to predict: washing efficiency and to generate washing curves, cake and filtrate composition, and residual cake moisture content and composition.

Mefenamic acid and paracetamol were selected as representative test compounds. Three different crystallization solvents were used for mefenamic acid and for paracetamol case, with relative structurally-related impurities deriving from synthesis.

As first stage of the optimization workflow, a model validation approach has been used to estimate cake properties (e.g. specific cake resistance, cake volume, cake composition after washing, washing curve). The data used for validation was generated via small-scale batch pressure filter experiments. Following on, the validated model was used to explore the design space and aid in the set-up of the optimization entity decisions. The optimization problem was then configured to reduce the impurity concentration in the final cake after washing. The findings from this were translated to a final model to simulate the optimal operating point.

1. INTRODUCTION

Pharmaceutical industry is starting to consider approaches to improve green metrics of drug manufacturing. Based on the 2017 Pharma 4.0 initiative [1], recent manufacturing research activity has been directed to move pharmaceutical manufacturing from a mostly empirical basis to be predominantly digitally driven [2], by using predictive tools to optimise process conditions to reduce product variance. To align pharmaceutical manufacturing with sustainable industry goals, a combination of modelling, online measurement and advanced control techniques are vital to predict product property outcomes, monitor and control processes and reduce the risk of non-conforming products [3,4].

Whilst a few examples of modelling integrated continuous unit operations using flowsheet models [5-10], have been published, these are mainly focused on secondary drug product manufacture rather than API synthesis, crystallisation, and isolation [11]. A detailed list of models already developed to simulate filtration and washing as standalone unit operations is reported in the conference proceeding 3001065, entitled “Integrated filtration and washing modelling of active pharmaceutical ingredients and impurities”.

The approach proposed in this work considers the isolation as integrated unit operation, where filtration and washing are modelled using the input slurry composition generated during the crystallization upstream process. The novelty proposed in this work is the capability to simulate washing process considering the key washing mechanisms observed in real processes: diffusion-dispersion with dilution and solid phase dissolution.

In 2009, Ruslim et al. [12] tried to modify the classical washing model, in order to study cases where the API is soluble in mother liquor and wash solvent because product loss during washing is an important parameter to consider. However, this work mainly considers the variation of the wash curve, without considering the possibility to use the model as tool to predict particle size variation caused by agglomeration/dissolution/deposition. So far only empirical approaches were studied to investigate the role of solvents, particle characteristics, and process conditions [13-16] on agglomeration, dissolution of the solid phase during washing [17], and deposition during washing [18].

The washing model proposed here allows the possibility of cake and impurity dissolution during washing. This case presumes that kinetic aspects can be neglected, and solid-liquid equilibrium is reached instantaneously. The system shows vertical heterogeneity and there is a composition gradient along the cake height.

To validate the scenarios described using the integrated models, mefenamic acid (MA), in combination with a series of crystallization and wash solvents, in presence of related impurities was selected as the test compound. A combination of predicted and empirical parameters was used as prediction input parameters. The data used for the validation stage were produced with small-scale batch pressure filter experiments.

The validated model was then used to simulate an integrated filtration and washing process with the view to maximize purity of the isolated material via optimization. This is essential to design the isolation process capable to remove residual impurities dissolved in the mother liquor [19-20]. The isolation optimization stage is also required to minimize

residual crystallization solvent commonly responsible for particle agglomeration and lumping during the downstream drying process [21].

Overall, the objectives of the models were to:

- Develop a robust model through rigorous model validation for filtration modelling as well as both displacement and diffusion-dispersion mixing during washing.
- Identify the product purity reached with a fixed wash ratio.
- Conduct a design space exploration to understand the critical process parameters affecting the critical quality attributes.

2. APPROACH

2.1 MATERIALS

The compound (mefenamic acid, 99%) and its impurities (copper (II) acetate (98%), 2-chlorobenzoic acid (98%), 2-3-dimethyl-n-phenylaniline (99%) and benzoic acid (99.5%)) were sourced from Sigma-Aldrich. The crystallization solvents used include ethyl acetate (99%, Alfa Aesar) and diglyme (99%, Alpha Aesar), whereas the wash solvents used were n-heptane (99%, Alfa Aesar) and cyclohexane (99%, Alpha Aesar).
The HPLC mobile phase was prepared with water (HPLC grade, VWR), ammonium phosphate (98%, Sigma-Aldrich) and ammonium hydroxide with concentration of 3M, acetonitrile (HPLC grade, VWR), tetrahydrofuran (99.9%, Sigma-Aldrich).

2.2 METHODS

2.2.1 ISOLATION PROCEDURE

A modified Biotage VacMaster was used for conducting filtration and washing of the suspensions using manual best practice. A detailed description of the unit is reported elsewhere [22].

Mefenamic acid (MFA) suspension was prepared using 2, 3-dimethelaniline, copper (II) acetate hydrate, 2-chlorobenzoic acid as representative synthesis impurities. The input stream composition is reported in

Table 1.

Table 1 Input stream composition for the two different mefenamic acid suspension: ethyl acetate and diglyme-water.

Ethyl acetate		Diglyme-water	
Input stream composition	**Mass fraction**	**Input stream composition**	**Mass fraction**
Ethyl acetate	0.876	Diglyme	0.052
Mefenamic acid	0.097	Water	0.006
2-chlorobenzoic acid	0.009	Mefenamic acid	0.141
Cu (II) acetate	0.008	2-chlorobenzoic acid	0.012
2-3-dimethyl-n-phenylaniline	0.01	Cu (II) acetate	0.012
		2-3-dimethyl-n-phenylaniline	0.014

2-3-dimethyl-n-phenylaniline (DMA), copper (II) acetate hydrate, and 2-chlorobenzoic acid (CBA) were initially dissolved into the selected crystallization solvent. The amount of mefenamic acid required to saturate the solvent solution was then added and dissolved.

The amount to get 10%w/w solid load of mefenamic acid was finally added to generate the suspension. The solid phase is added to the saturated solution to mimic the slurry obtained after crystallization. In case the saturated solution was prepared with diglyme, specified amount of water was added in accordance to the synthesis liquor. For diglyme the weight ratio between diglyme: water was 89:11.

To avoid “antisolvent effect”, leading to dissolved active pharmaceutical ingredient being precipitated during the first wash step, the first stage wash was prepared using a mixture of pure crystallization and wash solvents equal to 10% of crystallization solvent and 90% of wash solvent (V/V). This mixing was not included in the displacement wash model however it was included in the diffusion-dispersion wash model.

2.2.2 FEED SUSPENSION AND ISOLATION MATERIAL CHARACTERIZATION

The characterization techniques used for the feed suspension and isolation material characterization are described in detail in conference proceeding 3001065. In summary:

- Mefenamic acid particle size distribution was analyzed with using a wet dispersions using laser diffraction (Mastersizer 3000 laser diffraction particle size analyzer with hydro dispersion unit, Malvern Panalytical, UK).
- The solubility of mefenamic acid in the crystallization and wash solvents mixture was predicted using COSMO*Therm* (COSMOlogic GmbH & Co. KG, Germany) [23].
- Calibration curves for pure mefenamic acid and 2-chlorobenzoic acid were gathered using a multilevel calibration method. Mobile phase for the HPLC analysis was prepared in accordance with European pharmacopeia [24].
- Offline sample characterization followed a precise sequence to prevent destruction of material required for further characterization
- Cake and filtrate masses were weighed at the end of each batch experiment.
- The impurity content in filtrates and cake was determined using the HPLC quantitative method.

2.2.4 MODEL DEVELOPMENT

An integrated filtration and washing model in the most sophisticated way was developed here. Filtration was simulated to stop at dryland and, to get washing simulations resembling a real process, diffusion-dispersion with solid phase dissolution were considered as washing mechanisms.

2.2.4.1 FILTRATION MODEL

Dead end filtration is the most common method of filtration, and can be studied by using different models. The simplest model is the conventional cake filtration theory [25].
Cake porosity (ε) is the fraction of the bulk volume of the cake that is occupied by pore/void space and can be defined as:

$$\varepsilon = 1 - \frac{V_s}{V_{cake}} \quad (1)$$

Where V_s is the volume of solids and V_{cake} is the volume of the cake. In general, specific cake resistance of a filter cake is defined as the resistance of fluid to pass through the cake. In accordance to Carman-Kozeny equation [26], cake resistance is related also to cake porosity:

$$\alpha_{av} = \frac{180\,(1-\varepsilon)}{\rho_s x_{sv}^2 \varepsilon^3} \tag{2}$$

Cake porosity is independent of particles size, but it is a function of particles size distribution, as explained above. Other approaches are commonly used to determine cake resistance as a function of the particle size distribution (PSD) and to the shape of particles [27].

The approximation used in these models are reported in Table 2.

Table 2 Assumptions used for filtration model.

Assumption / approximation	Description
Cake resistance equation – particle size	Particle size used corresponds to a single particle size, the volumetric mean diameter
Cake resistance equation – particle shape	Carman Kozeny equation does not consider particles aspect ratio as parameter that affects cake resistance; other approaches [28] consider shape and texture of particles can be represented by a fractal structure or aspect ratio distribution

The cake resistance can be then used to calculate filtrate flow rate, along with media resistance and other filtration parameters by using the Darcy's law for constant pressure [26]:

$$\frac{dV}{dt} = \frac{A^2\,\Delta P}{\mu\,(\alpha_{av} c V + A R_m)} \tag{3}$$

Filtration process was simulated using gPROMS filtration model, where Carman-Kozeny theory was used.

Filtration was modelled as a batch process, considering the Stoke's law sedimentation equation and sedimentation process occurring during filtration. Filtration process ends at dryland point.

2.2.4.2 WASHING MODEL

This model describes a washing process where the initial wet packed bed obtained by filtering a suspension to dryland is washed by diffusion-dispersion with dissolution mechanisms. Diffusion and dispersion washing can be modelled using the main and side channel model [29-30]. The assumptions used in this model are reported in Table 4.

Table 3 Assumptions used for diffusion dispersion washing model.

Assumption/approximation	Description

Mass transfer washing period	Side channels are totally filled with residual filtrate. Part of the solute may be flushed out by the initial charge of wash filling the main channels when the cake is fully saturated prior to the onset of washing
Diffusional displacement	Occurs during the mass transfer stage to remove filtrate from side channels. Filtrate is removed from side channels and leaves the cake by plug flow in the main channels
Mixing between mother liquor and wash solvent	Instant process (as assumed in model 1b). Since the mixing time between wash solvent and mother liquor is approximated to zero, the diffusion coefficient used for model 1c is very small (fixed to $1*10^{-9}$) [31, 32-33]
Cake layer composition	• Layer 1 corresponds to liquid phase near to the surface of the cake, while layer 10 is the layer near the filter media. At the beginning of the washing process layer 1 is made of pure wash solvent, while layer 10 is made of pure mother liquor. • Liquid composition of each layer is changing following the binary plot solubility curve in layer 10 the liquid composition gradually moves from pure mother liquor to pure wash solvent.

As reported by Tien (2012) [31], washing can be considered as a mass transfer process taking place in porous media. However, considering diffusion and dilution washing, wash solvent diffusion in mother liquor needs to be considered. Considering a homogeneous medium, with a uniform pore liquid flow rate and the diffusion-dispersion effect limited in the flow direction:

$$D_L \frac{d^2c}{dx^2} - \frac{u_s}{\varepsilon_{av}} \frac{dc}{dx} = \frac{dc}{dt} \tag{4}$$

For the initial conditions of:

$$c_j = c_{j,i} \quad x > 0 \quad t < 0 \tag{5}$$

And boundary conditions (assuming axial dispersion effect is ignored at the top of the cake):

$$\begin{aligned} c_j &= c_{j,w} \quad x = 0 \\ \frac{\delta c_j}{\delta x} &= 0 \quad x \to \infty \end{aligned} \tag{6}$$

This model was implemented considering the washing process simulated with a cascade of 10 well-mixed crystallisers where the approach used to mimic the dispersion washing mechanism modelled with the PF approach is clearly described by Levenspiel (1998) in the compartment models chapter 12 [34]. The 10 different reactors were modelled in series with dimensions equivalent to the cake volume predicted in the filtration model (mL). To investigate solid phase dissolution, this model describes washing as 10 layers of solvent of varying composition where in each layer instant mixing of the two liquid phases occurs.

The liquid composition in each layer evolves over time from pure mother liquor to pure wash solvent.

2.2.4.3 MODEL VALIDATION, OPTIMIZATION AND DESIGN SPACE EXPLORATION

3 RESULTS, INTERPRETATIONS AND DISCUSSIONS

3.1 EXPERIMENTAL RESULTS

The experimental results are already described in conference proceeding 3001065. The same experiments were used to validate the filtration and washing model here described. The table below summarises the experiments used to develop the model.

Table 4 Mefenamic acid experimental filtration and washing results.

Experiment Number	Crystallization Solvent	Wash Solvent	Cake Resistance (m/kg)	Medium Resistance (1/m)
1	Ethyl acetate	Cyclohexane	$1.23x10^8$	$3.48x10^9$
2	Diglyme-water	Heptane	$4.73x10^8$	$7.39x10^9$
3	Ethyl acetate	Heptane	$1.84x10^9$	$1.35x10^{10}$
4	Ethyl acetate	Heptane	$9.84x10^7$	$2.98x10^9$
5	Diglyme-water	Cyclohexane	$9.24x10^8$	$1.21x10^9$
6	Diglyme-water	Cyclohexane	$1.01x10^8$	$3.96x10^9$
7	Diglyme-water	Cyclohexane	$6.54x10^8$	$3.19x10^9$
8	Diglyme-water	Heptane	$6.69x10^8$	$1.85x10^9$
9	Diglyme-water	Cyclohexane	$1.46x10^8$	$4x10^9$

3.2 MODEL DEVELOPMENT

In first instance, a parameter estimation was performed to identify optimal particle (sphericity), cake (porosity and compressibility index) and filtration characteristics (medium resistance) to fit experimental filtration performance. These estimated parameters were then used to simulate filtration and washing using the diffusion-dispersion modelling approach. This was further developed to include impurity removal and dissolution of the crystal phase in the diffusion-dispersion model. The kinetic parameters for dissolution and impurity removal/inclusion within the model allow for the purity of the crystallized solid phase to change. These were estimated and used to simulate washing performance with the aim to reduce impurities in the solid phase. As a final step, a layer-by-layer analysis of the solid phase was modelled to understand the distribution of the API and impurities in the cake.

3.3 PARAMETER ESTIMATION

A detailed analysis of the parameter estimation for filtration kinetics is presented in conference proceeding 3001065. A summary table is presented below.

Table 5 Estimated cake and filtration parameters estimated for the different mefenamic acid case systems.

Crystallization Solvent	Wash Solvent	Expt Ref	Carman-Kozeny Sphericity	Cake Porosity	Medium Resistance (1/m)	Compressibility Index
Diglyme-water	Heptane	2, 8	0.526	0.694	$1.31x10^8$	0.833

Diglyme-water	Cyclohexane	5, 6, 7, 9	0.4964	0.5258	$1.31x10^7$	0
Ethyl acetate	Heptane	3, 4	0.4134	0.4804	$1.6x10^9$	1.312
Ethyl acetate	Cyclohexane	1	0.399	0.476	$1.46x10^9$	0

In general, the estimated cake and filtration parameters using cake and filtration parameters matching the experimental cases reported in Table 5, show a good fit with the experimental data. The simulated compressibility value estimated for the systems with cyclohexane as the wash solvent were zero. This may be either due to the cake being incompressible or that the data was not sufficient to estimate the cake compressibility. The other two systems estimated compressibility indices from the simulation within the Darcy's Law range.

3.4 MODEL VALIDATION

This section presents the validation results for dissolution and impurity inclusion kinetics for the diglyme-water cyclohexane system. Table 6 summarises the results for Experiments 6, 7 and 9 for the respective final cake compositions.

Table 6 Comparison between mefenamic acid experimental data and simulated data obtained with diffusion-dispersion model with dissolution and impurity inclusion kinetics.

Experiment	MFA Mass Fraction (kg/kg)		CBA Mass Fraction (kg/kg)		DMA Mass Fraction (kg/kg)	
	Measured	**Predicted**	**Measured**	**Predicted**	**Measured**	**Predicted**
6	0.841	0.809	0.0796	0.0957	0.0796	0.0957
7	0.853	0.837	0.0736	0.0816	0.0736	0.0816
9	0.844	0.831	0.0780	0.0845	0.0780	0.0845

The results show good predictive capability for the final cake composition, with most values falling within ±10%. This is consistent with expectations, where the diffusion-dispersion wash mechanism coupled with dissolution and impurity inclusion kinetics is the most sophisticated model-driven approach to estimate final cake composition. The error in most cases is an underprediction. This can be related to both human error (washing process stopped over dryland point, with potential desaturation of the cake and extra impure filtrate removed) and/or lack of intermediary points to develop a robust mechanistic model. In practice, the filtration equipment used make the collection of small aliquots of the overall filtrate removed difficult with consequent impossibility to track the evolution of impurity removal at different wash ratios. Further details of the equipment and procedures used to filter and wash the samples produced are reported elsewhere [21]. One possibility to achieve this is to use constant rate washing mechanism [35]. Overall, for the purposes of this work, the results are within an acceptable error range.

3.5 DESIGN SPACE EXPLORATION

Design space exploration was conducted to determine the model parameters that affect the impurity removal during washing. The quality attributes being studied were the API and impurity concentrations in the solid phase of the cake. The design space exploration also included a sensitivity analysis to understand which process parameters affect washing performance, specifically when considering impurity removal. Figure 1 and Table 7 show the results from the design space exploration and the sensitivity analysis respectively. Ottoboni et *al.* (2019)[22] reported that volume and nature of wash solvent

used, and the number of washes done affect the capability to remove impurities. Figure 1 shows the results from the two design space explorations conducted, displaying the wash volume against impurity concentration in both figures for the diglyme-water cyclohexane system. Figure 1(a) and (b) show the effect of a single wash on the impurities (CBA) in the liquid and the solid phases respectively. In both cases, a higher wash volume leads to a lower impurity concentration in the filtrate and the final cake respectively, which is expected. The graphs also show that beyond 30mL (or 4 equivalent cake volumes), the change in impurity concentration for every additional mL of wash solvent used decreases exponentially. Therefore, after that amount of wash solvent the purity does not improve consistently, and any extra amount of wash solvent use is just extra wastage produced. Figure 1 (c) shows the effect of multiple washes, where in Figure 1(c)(i) the residual impurity concentration is simulated in case of 2 washing stages, while in Figure 1(c)(ii), the residual impurity concentration obtained after 3 washes is simulated. For all of these simulations, the initial wash set up using a wash volume of 17mL. Wash solvent volume and washing time for wash 2 and 3, instead, was varying for subsequent washes. Figure 1 (c) shows that there is an inverse relationship with the number of washes and purity of the solid cake: in general, the purity of the cake decreases with every additional wash. The graph also shows that lower wash volumes lead to a higher cake purity. This is contrary to what is expected because multiple washes and larger volumes should lead to a cake with higher purity. The effect of higher wash volumes is clearly seen in Figure 1(a) and (b). The difference seen in Figure 1 (c) can be due to two reasons. Firstly, only two experimental values are available for the solid phase composition – the start of the first wash and the end of the isolation process, which includes drying. For simplicity, it is assumed that no changes occur in the cake during drying, however this may not be the case since the elevated temperatures during drying can lead to unwanted dissolution and/or growth of the cake. Secondly, the solubility of the impurities is not considered in the model. That is, the impurity growth kinetics are described as a factor of the growth kinetics of the API and therefore the solubility of the API is also indirectly linked to the solubility of the impurities. In reality, the solubility of the impurities is much higher in the wash solvent chosen in all cases. This would lead to lower dissolution in the wash solvent and ultimately a higher impurity concentration in the final cake.

Following on from the results of the design space exploration, a sensitivity analysis was conducted to further refine the critical process parameters that would highly affect the quality attributes. It was found that the cake purity was highly dependent on 2 factors – the composition of the first wash, and the volume of subsequent washes. This was used as a guide to define the optimization objective function, decisions, and constraints.

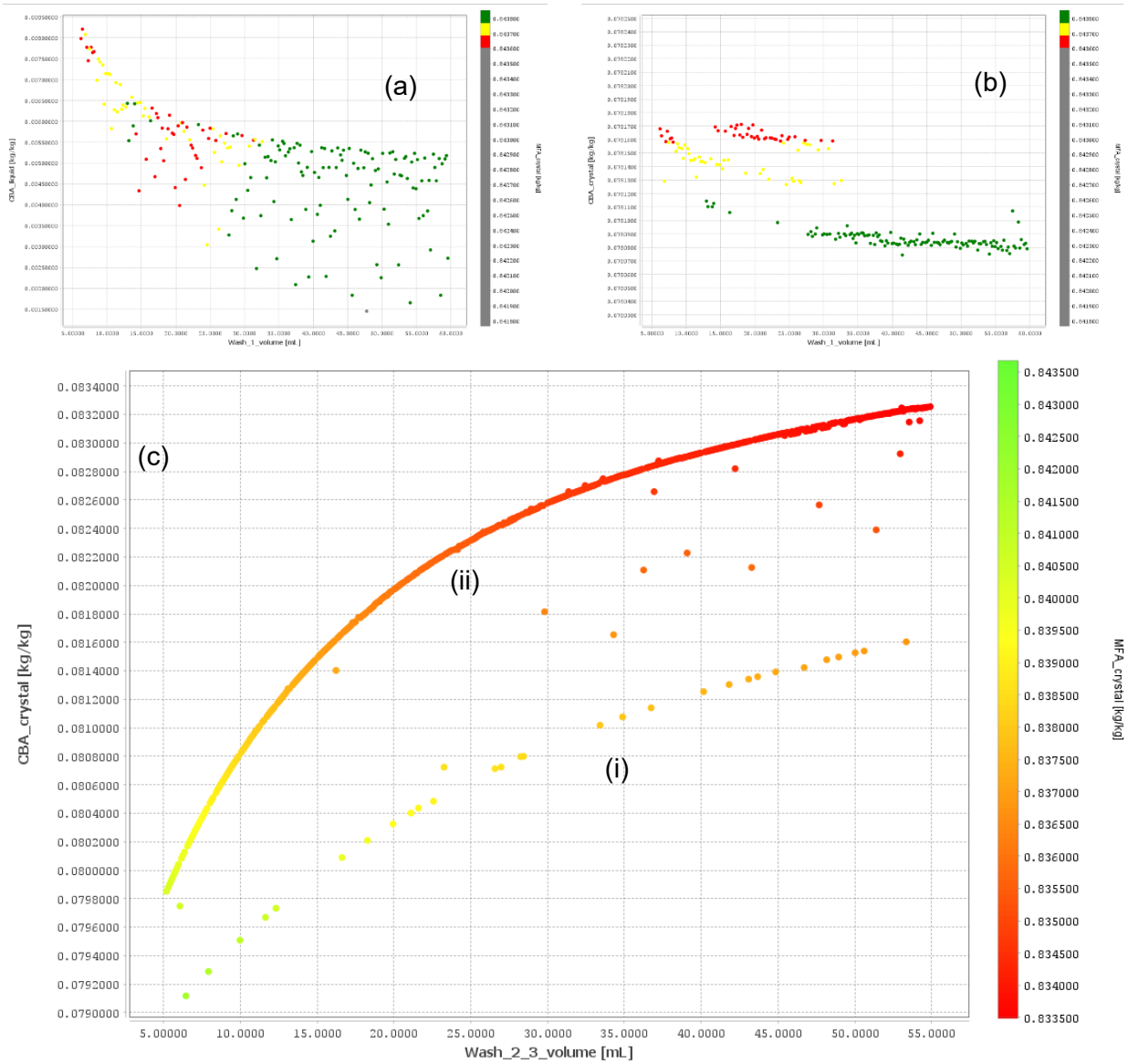

Figure 1 Design space explorations: wash volume used against impurity concentration (CBA) (green (high purity) to red (low purity)) for (a) liquid phase and (b) solid phase for a single wash cycle and (c) crystal phase for multiple wash cycles for the diglyme-water and cyclohexane system.

3.6 OPTIMIZATION

Based on the results from the sensitivity analysis, the washing model was optimized to maximise the crystal purity while reducing the washing volume and number of washes being used. The objective and constraints for each optimization run are described below:

- Optimization 1 – The objective was to maximise final cake purity. The liquid composition of the first wash was fixed, while the time and volume for each wash was varied, with the same volume being used for the second and third washes
- Optimization 2 – The objective was to maximise final cake purity. The liquid composition of the first wash was varied along with the time for each wash. However, the wash volume was fixed at the values displayed below for each wash. These values are based off experimental results from the diglyme-water cyclohexane system.
- Optimization 3 – The objective function was to minimize wash volume use. The liquid composition for the first wash was fixed, while the time and volume for each wash was varied. Additionally, a constraint was added to have the final cake purity greater than 84%.

Table 7 below summarises the outputs of three different optimization results.

Table 7 Results from 3 different optimization runs

	Optimization 1	**Optimization 2**	**Optimization 3**
Crystal Purity (%)	84.3616	84.3568	84.1955
Mass fraction cyclohexane (kg/kg)	0.1	0.395	0.1
Mass fraction diglyme-water (kg/kg)	0.9	0.615	0.9
Wash volume 1 (mL)	28.95	17	6
Wash volume 2 and 3 (mL)	16.05	16	6
Charge time wash 2 (s)	2.15	9.67	20
Charge time wash 3 (s)	9.81	20	60.03
Simulation duration (s)	12	80.65	80.16

The three optimizations show that there is a trade-off between the different process parameters. For instance, if there were no material constraints, it is possible to achieve the highest cake purity (84.36%) by using a total of approximately 75 mL of wash solvent. Similarly, if there was a material constraint, you can achieve a marginally lower cake purity (84.2%) by using just 18 mL of wash solvent, albeit while taking much longer for the same purity to be achieved (12s vs 80s).

3.7 CAKE LAYER ANALYSIS

The diffusion-dispersion with dissolution model developed here was also used to analyse different cake layers within the final cake. This was done by assuming 10 different layers for the cake, where the top-most layer (Layer 10) would be introduced to the wash solvent first, followed by the next (Layer 9) all the way to the final layer (Layer 1), where the wash solvent would reach already mixed with the impure mother liquor and therefore with less efficacy in removing impurity after going through the first 9 layers.

Figure 2. Cake layer analysis showing the initial (blue) and final (green) solid phase composition of each layer from point of wash introduction at the top (layer 10) to the bottom-most layer (layer 1)

Figure 2 shows the results from the cake layer analysis for the diglyme-water cyclohexane system. The results clearly indicate that the top-most layer of the cake has the highest purity (highest content of MFA), and that decreases until the bottom-most layer, where the impurity concentration is higher (highest content of CBA and DMA). This is what would be expected, because Layer 10 would be in contact with the purest wash solvent for relatively the longest time, hence allowing for better washing at this layer. As the wash solvent moves further down, it would be contaminated with a relatively higher concentration of impurities when compared to the previous layer, reducing its effectiveness in removing more impurities. This finally leads to a wash solvent with the highest concentration of impurities as it approaches the final layer, therefore it is unable to wash away further impurities at this stage. To purify the last layer of the cake (Layer 1) larger quantities and multiple aliquots of wash solvent are required.

4 CONCLUSIONS

To facilitate process development of APIs without extensive experimental work, a digital tool capable of transferring material property information between unit operations to predict the product attributes in integrated purification processes has been developed.
A mechanistic model-based workflow for the optimization of an integrated filtration and washing model was developed to minimize impurities in the isolated cake. This workflow procedure first estimates product and process characteristics (e.g. particle sphericity, porosity, cake and medium resistance, and cake compressibility) using a gPROMS FormulatedProducts Carman-Kozeny filtration model with filtration stopped to dryland. For model validation, a series of experiments were used with mefenamic acid and its related impurities in a series of different crystallization and wash solvent. Overall, the estimated cake and filtration parameters using cake and filtration parameters matching the experimental outcomes (cake and medium resistance). In general, the estimated cake compressibility was in the Darcy's Law range. The model allowed for a quick and relatively accurate calculation of the cake compressibility index, which would have taken much longer to obtain experimentally.

The estimated product and process parameters were then used to simulate filtration and washing using the diffusion-dispersion modelling approach, including dissolution and impurity inclusion kinetics. The filtration and washing data used for the model comparison with the experiments was the concentration of the mefenamic acid (MFA), 2,3-chloro benzoic acid (CBA), and 2-3-dimethyl-n-phenylaniline (DMA) present in the final cake. Overall, the predicted and measured cake compositions were within ±10%.

This was then used for design space exploration (using the Global Systems Analysis approach) to identify which washing conditions (first wash composition, wash solvent volume, and number of washing stages) reduce the impurity concentration in the final cake after washing. Overall, no correlation between the time of wash to the impurity concentration was observed, however a strong correlation was seen between wash solvent volume used and purity achieved. In general, a higher wash solvent volume use resulted in a lower amount of residual impurity left in the washed cake. The sensitivity

analysis performed showed that the composition of the first wash and the volume of subsequent washes had a significant effect on the purity of the final cake. These findings were used to simulate three different optimizations, showing how material and/or time constraints would affect the final cake purity.

As a final step, a layer-by-layer cake analysis was simulated to predict the cake composition at different layers during washing. For this, the cake was “split” into ten different layers, with the wash solvent introduced to the top-most layer (Layer 10). The results indicated that the top-most layer of the cake has the highest purity, and that decreases until the bottom-most layer (Layer 1), where the impurity concentration is higher.

ACKNOWLEDGEMENTS

The authors would like to acknowledge that this work was carried out in the CMAC National Facility housed within the University of Strathclyde’s Technology and Innovation Centre and funded with a UKRPIF (UK Research Partnership Institute Fund) capital award (Grant Ref: HH13054) from the Higher Education Funding Council for England (HEFCE).

The author wishes to acknowledge the contribution of all the colleagues and our funders:

- Bhavik Mehta: Development of an Advanced Modelling System for Active Ingredient Pharmaceutical and End-to-End Manufacturing Processes (Innovate UK KTP Ref. 11937)
- Cameron Brown and Sara Ottoboni: EPSRC Future Continuous Manufacturing and Advanced Crystallisation Research Hub (UKRI Grant Ref. EP/P006965/1)
- Sara Ottoboni: visNET: Virtual in situ networking to reinvent the rules of international collaborations and reduce gender differences in academic careers (UKRI Grant Ref. EP/S012079/1)

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