INTEGRATED FILTRATION AND WASHING MODELLING OF ACTIVE PHARMACEUTICAL INGREDIENTS AND IMPURITIES

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ABSTRACT
There is an increasing interest in the application of continuous processing technologies in pharmaceutical manufacturing to control crystal properties and deliver consistent particulate products. The focus of the work reported here is to combine 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 track impurities in the liquid phase.

A Carman-Kozeny[1] filtration model is integrated with a custom diffusion with axial dispersion washing model[2,3]. The custom washing model assumes no solid phase dissolution or precipitation. To mimic the dispersion washing mechanism, a single stage continuous stirred-tank reactor approach was used.

Mefenamic acid was selected as a representative test compound. Three different mefenamic acid crystallization solvents with relative structurally-related impurities deriving from synthesis were selected. Two wash solvents were selected, n-heptane and cyclohexane. The objective of the models was to a) identify the product purity reached with a fixed wash ratio, and b) explore the design space in order to understand the process conditions to potentially minimize impurity content in the isolated cake.

Two different filtration halting procedures were simulated: filtration halted to dryland. 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.

To validate the scenarios described using the integrated models, some experimental data measured from the biotage filtration unit was used. To validate the cake and filtrate composition during filtration and washing stages, HPLC quantitative method was used. As a precursor to optimization, a Global Systems Analysis was conducted to explore the design space and aid in the set-up of the optimization entity decisions.

1. INTRODUCTION

The pharmaceutical industry is starting to adopt continuous active pharmaceutical ingredient manufacturing to reduce production costs, improve manufacturing flexibility, reduce infrastructure costs, reduce manufacturing lead time and to improve sustainability[4,5]. A further driver is reduction of variance in API quality critical attributes[6,7]. Typically, desired product attributes to achieve after purification (crystallization and isolation) are particle size, habit, and purity[8]. 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 through to formulation[9]. To achieve this, 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[5, 10]. Another challenge the pharmaceutical industry faces is reducing the quantity of material consumed during process development[11-12]. Digital design of continuous API manufacturing offers a path to achieving this. This includes modelling and predicting process performance as a function of the operating conditions for both individual continuous unit operations and for the integrated processes with the aim of optimizing process design and reducing the laboratory time and cost needed to develop new products. While a few examples of modelling integrated continuous unit operations using flowsheet models have been published[13-15], these are mainly focused on secondary drug product manufacture rather than API synthesis, crystallization, and isolation[16].

Classical isolation models do not consider integrated filtration and washing processes because they are seen as two separate process operations modelled using two different models. Dead end filtration can be studied by using different models, but the common model used is the conventional cake filtration theory[17]. Conventional filtration theory describes the relevant continuity equations, the closing relationship and the appropriate initial boundary and moving boundary conditions[17-18] of a filtration process. Further description of the existing filtration models was in detailed reviewed by Wakeman et al. (1991)[19] and Nagy et al. (2020)[20].

One of the first washing models developed was proposed by Rhodes (1934)[21-22] which described the variables affecting the washing curve. Different behaviors are observed according to the nature of mother liquor and wash solvent[23]. In general, it appears that when the mother liquor has a strong wetting preference for the solid, the wash solvent tends to occupy the largest pores and the mother liquor occupies the finer ones. Thus, there may be two separate networks, each containing its own fluid phase. This behavior was described by the main and side channel model[3, 22, 24], that is used to describe the displacement-diffusion with axial dispersion model. Another approach to predict the washing curve is by considering a washing process driven by displacement, diffusion and dilution washing is reported by Svarowsky (2001)[25] and Wakeman and Attwook (1988)[26-27]. As reported by Tien (2012)[3], 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. Jarvelainen and Norden (1968)[28], Backhurst et al. (1999)[29], and Arora et al. (2006)[30] discussed the effect of Peclet number and diffusivity coefficient on the shape of the wash curve.

The work here proposed combines filtration and washing operations commonly used in API purification and isolation by combining predicted and experimental data generated during upstream crystallization process. 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[31-32]. The isolation optimization stage is also required to minimize residual crystallization solvent commonly responsible for particle agglomeration and lumping during the downstream drying process[33].

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.

Different washing modelling scenarios (displacement or diffusion-dispersion washing) were validated to identify key process parameters (e.g. wash solvent volume and number of washes used) and their effect on filtration and washing responses. Model validation was used to identify which level of the model was capable to describe the experimentally observed isolation data.

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

From the mefenamic acid test compound a total of 9 experiments were used for the parameter estimation (PE) and external model validation (V) of the model. The filtration and washing factors used for these experiments is reported in Table 1.

Table 1 Filtration and washing parameters used for the mefenamic acid experiments. Experiment 6, 7, and 9 are replica of the same filtration and washing conditions.

Expt Ref Paper	PE or V	Crystallization Solvent	Wash Solvent	Isolation Pressure (mbar)	Volume of Wash Solvent (equivalent 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

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[34].

Mefenamic acid 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 2.

Table 2 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
		Cu (II) acetate	0.012
2,3-dimethylaniline	0.01	2,3-dimethylaniline	0.014

2, 3-dimethelaniline, copper (II) acetate hydrate, and 2-chlorobenzoic acid 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 CHARACTERIZATION

A series of raw material characterization were conducted to investigate:

- The particle size distribution (PSD) of the mefenamic acid material used to generate the slurry. 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 method parameters used for the samples analysis were as follows: mefenamic acid particles were dispersed in heptane using a Hydro MV cell

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(Malvern Instruments Limited, UK) by adding particles to the cell to reach a laser obscuration of approximately 15%. Three measurements were taken for each sample. Measurements were made with and without ultrasound to detect and prevent agglomeration. Laser diffraction measurements are expressed as the volume-weighted distribution of equivalent sphere diameter.

- The solubility of mefenamic acid in the crystallization and wash solvent mixtures was predicted using COSMO*Therm* (COSMOlogic GmbH & Co. KG, Germany)[35].
- 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 to European pharmacopeia[36]. An Agilent 1260 Infinity II system with diode array and RI detector was used. The column was an Agilent Eclipse Plus C18, 4.6x250mm, 5µm, P/N 959990-902 operated at 25°C, with a flow rate of 1mL/min. The injection volume was 10µL, wavelength: 254nm, the mobile phase was 23:20:7 of acetonitrile: buffer solution: THF. Calibration curves of 2,3-dimethylaniline and cooper(II) acetate were not determined as the two compounds appeared to be insoluble in the mobile phase.

2.2.2 ISOLATION MATERIAL CHARACTERIZATION

Offline sample characterization followed a precise sequence to prevent destruction of material required for further characterization:

- Cake resistance and media resistance and filtration flow rate. Data were collected manually measuring the time required to collect a series of filtrate volumes removed during filtration. 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

The integrated filtration and washing models were generated using gPROMS FormulatedProducts.

The integrated filtration and washing model was developed in 3 stages:

1. Filtration is modelled as a batch process, using a batch pressure filter. Filtration stops at dryland, leaving the cake pore saturated with mother liquor.
2. Filtration and washing are modelled using a continuous pressure filter, where washing stages are done after filtration. The filter is simulated to mimic the operative procedure of the biotage unit.
3. One of the assumptions used in model stage 2 is that the process that governs washing is displacement of mother liquor.
   Another assumption considered for the washing model is that no changes in solid phase are considered (no particle dissolution or growth).
4. Washing is simulated with mixed-suspension, mixed-product-removal (MSMPR) crystallizer in well-mixed liquid phase conditions to mimic diffusion dispersion, operating in semi-batch mode.
   The assumption considered for the washing model is that no changes in solid phase are considered (no particle dissolution or growth).

The equation used for the filtration and customized wash model are below described.

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[37]. Cake porosity is the fraction of the bulk volume of the cake that is occupied by pore/void space and can be defined as:

$$\varepsilon = 1 - \frac{V_s}{V_{cake}}$$ (3)

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[38], cake resistance is related also to cake porosity:

$$\alpha_{av} = \frac{180\,(1 - \varepsilon)}{\rho_s x_{sv}^2 \varepsilon^3}$$ (4)

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 in accordance to the particle size distribution (PSD) and to the shape of particles[39].

The approximation used in these models are reported in Table 3.

Table 3 Assumptions used for filtration model.

Assumption / approximation	Description
Cake resistance equation – particle size	Particle size used corresponds to singles 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[40] 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[38]:

$$\frac{dV}{dt} = \frac{A^2 \Delta P}{\mu\,(\alpha_{av} cV + AR_m)}$$ (5)

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

Below are reported the equation used for the displacement and for the diffusion dispersion washing models.

The initial condition was taken as the end of a filtration stopped at dryland, i.e. a cake saturated with crystallization mother liquor.

The wash ratio, W_r, was defined as the ratio between the volume of wash added, V_w, to the volume of voids in the cake, V_v. Wash ratio can also be related to time, t, by consideration of the superficial wash velocity, u_s, and cake height, L:

$$W_r = \frac{V_w}{V_v} = \frac{u_s t}{L \varepsilon_{av}} \tag{6}$$

In model approach 2, washing is governed by displacement mechanism, where the solid phase of the suspension is not interacting with the liquid phase and no dissolution or precipitation is occurring.

Displacement washing is a simplistic approach to model washing process which considers the volume of liquid within the filter cake as finite. Therefore, any wash added causes and equal removal of mother liquor. As no mixing between the wash and mother liquor is assumed, the liquid exit composition will remain constant (as the mother liquor composition) until the full volume of mother liquor in the cake has been displaced by the wash liquid. At which point the liquid exit composition will be that of the wash. This can be represented by the piecewise function:

$$c_{j,e} = \begin{cases} c_{j,i} & \text{if } W_r < 1 \\ c_{j,w} & \text{if } W_r \geq 1 \end{cases} \tag{7}$$

The washing approach 3 describes a washing process where the feed wet packed bed obtained by filtering a suspension to dryland is washed by diffusion dispersion mechanisms.

Diffusion and dispersion washing can be modelled using the main and side channel model[40]. The assumptions used in this model are reported in Table 4.

Table 4 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 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. Since the mixing time between wash solvent and mother liquor is approximated to zero, the diffusion coefficient used is very small (fixed to $1*10^{-9}$)[3, 37-38]

2.2.4.3 MODEL VALIDATION, OPTIMIZATION AND DESIGN SPACE EXPLORATION

Two set of validations were done for the filtration model to estimate:

- the media resistance and the Carman Kozeny cake resistance parameters, and the porosity based on initial guesses calculated from experimental data.
- the cake compressibility index, where data is available.

The estimation of these parameters is essential for the comparison of simulated and experimental filtration performances and therefore to determine the goodness of the model to fit experimental data. The estimated parameters will be then used to validate model approach 1, 2, and 3.

Model optimization was conducted for model approach 3. During the model optimization activity, two different set of simulations were done to explore the design space of the isolation process.

In the first approach, the first wash is set as the most significant washing process, and the aim of the design space exploration is to model the volume/time required to deliver a final solution with low levels of impurity. This approach allowed to identify the optimal amount of wash solvent to use during the first wash to maximize purity. Furthermore, this approach explored the threshold wash solvent volume required to get minimal change in solution concentration.

The second approach puts more emphasis on the second/third wash cycles and their effect on the impurity removal. This approach was used to identify the optimal amount of wash solvent to use during the second wash to maximize purity, and to get the amount of solvent after which no evident purity improvements are observed.

3 RESULTS, INTERPRETATIONS AND DISCUSSIONS
3.1 EXPERIMENTAL RESULTS

During biotage filtration and washing experiments done with mefenamic acid test compounds, cake resistance, medium resistance, and filtrate flow rate measured during filtration and washing experiments were measured. The results of cake and medium resistance are reported in Table 5.

Table 5 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	1.23×10^8	3.48×10^9
2	Diglyme-water	Heptane	4.73×10^8	7.39×10^9
3	Ethyl acetate	Heptane	1.84×10^9	1.35×10^{10}
4	Ethyl acetate	Heptane	9.84×10^7	2.98×10^9
5	Diglyme-water	Cyclohexane	9.24×10^8	1.21×10^9
6	Diglyme-water	Cyclohexane	1.01×10^8	3.96×10^9
7	Diglyme-water	Cyclohexane	6.54×10^8	3.19×10^9
8	Diglyme-water	Heptane	6.69×10^8	1.85×10^9
9	Diglyme-water	Cyclohexane	1.46×10^8	4.00×10^9

Comparable values of cake and media resistance were measured for the different samples. Slightly higher cake and medium resistance were observed for experiment 2 and 3, where the highest driving force was used (600mbar). As reported by Darcy[38] cake and medium resistance are correlated to the driving force used.

3.2 MODEL DEVELOPMENT

In first instance, a parameter estimation investigation was done to identify optimal particle (sphericity), cake (porosity and compressibility index) and filtration characteristics (medium resistance) to use to fit experimental filtration performance. These estimated parameters were then used to simulate filtration and washing using the two modelling approaches - with different mixing mechanisms which were

displacement or diffusion dispersion - and compare which model approach give cake composition after filtration and washing comparable with the experimental data.

The model approach capable to provide more accurate estimation of final cake composition after filtration and washing was then used for design space exploration. As reported in method section, two isolation model approaches were used to study the effect of different washing mechanisms: pure displacement and diffusion dispersion mechanisms. The continuous pressure filter model consists in a Carman Kozeny filtration halted to dryland, followed by pure displacement washing mechanism. The MSMPR washing model instead consists in a diffusion dispersion washing mechanism, washing feed information (cake composition) are provided by a decoupled Carman Kozeny filtration model where filtration stopped at dryland condition.

3.3 PARAMETER ESTIMATION

Parameter estimation for the different mefenamic acid case studies were done using the batch pressure filter model with filtration halted to dryland. Four different cases were studied using the same crystallization and wash solvent combinations and the same filter characteristics. These investigations allowed to estimate the cake and filtration properties to use for model validation and optimization. One of the estimated parameters, cake compressibility, is defined as the capability of the cake to be squeezed by the driving force applied during the filtration step. The equation used to calculate the compressibility index is reported elsewhere. In general, cake compressibility is calculated as the slope of the linear fitting natural logarithm of different cake resistance values with respect to the natural logarithm of the driving forces used to determine those cake resistances[37, 41]. The literature reports three different level of cake compressibility that are defined based on the value of n[42]: low and moderately compressible, n<1, high compressible, n>1, and extremely compressible, n>>1. The border between high and extreme compressibility is not well defined but n values for highly compressible solids are typically reported in the interval of 1-2[43]. Pharmaceutical cakes are generally low to moderately compressible, making them fit within the Darcy's law validity range for the compressibility index. The models therefore were also used to determine if the estimated values fitted the Darcy's law compressibility index range.

Table 6 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	1.31×10^8	0.833
Diglyme-water	Cyclohexane	5, 6, 7, 9	0.4964	0.5258	1.31×10^7	0
Ethyl acetate	Heptane	7, 9	0.4134	0.4804	1.6×10^9	1.312
Ethyl acetate	Cyclohexane	1	0.399	0.476	1.46×10^9	0

In general, the estimated cake and filtration parameters using cake and filtration parameters matching the experimental cases reported Table 5 , show 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 law range.

3.4 MODEL VALIDATION

Continuous pressure filter and MSMPR washing models were validated using the 9 experiments reported in Table 1 for mefenamic acid test compound. The filtration and washing data used for the model comparison with the experiments are filtration Darcy plot (volume of filtrate removed versus time) and the solvent mass removed during filtration and the concentration of the mefenamic acid and 2,3-chloro benzoic acid removed during washing, dissolved in the removed filtrate.
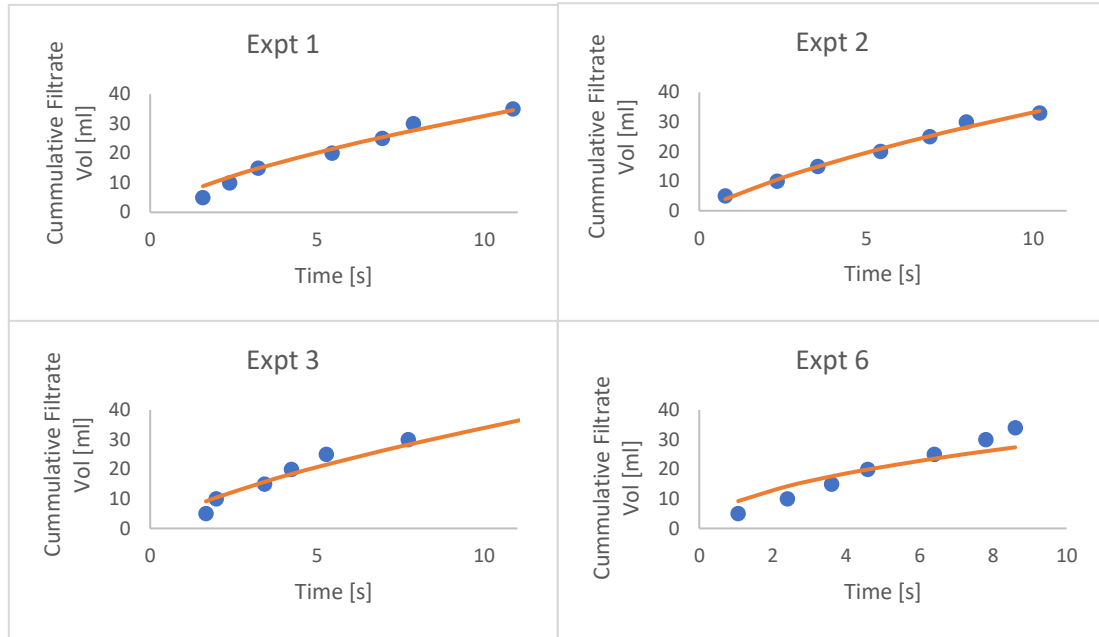
Figure 1 Experimental (blue circle) and simulated (orange line) cumulative volume of liquid phase removed during filtration for experiment 1, 2, 3 and 6.

Overall the simulated Darcy's plots reported in Figure 1 reproduce with a good accuracy, especially for experiment 1, 2, and 3 the filtration flow rate evolution. Less accuracy is observed for experiment 6, which can be attributed to errors in manually collecting the experimental data.

Table 7 Comparison between mefenamic acid experimental data and simulated data obtained with the pressure filter model and with the crystallizer model. The values correspond to the crystallization solvent mass removed during filtration and the concentration mefenamic acid (MFA) and 2,3-chloro benzoic acid (CBA) removed during the first wash stage.

Experiment number	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				
1	4.66E-03	1.36E-03	1.42E-03	1.79E-03
2	4.01E-03	1.19E-03	2.12E-02	2.33E-03
3	3.73E-03	9.56E-04	1.21E-03	2.48E-03
6	5.55E-03	1.36E-03	2.06E-02	4.74E-03
Displacement model				
1	1.93E-03	1.73E-03	1.10E-04	9.92E-05

2	7.18E-03	1.22E-03	1.54E-03	1.39E-03
3	2.06E-03	1.63E-03	1.47E-04	1.33E-04
6	3.55E-03	1.00E-05	2.28E-04	3.47E-05
Diffusion dispersion model				
1		2.74E-03	8.30E-04	7.47E-04
2		7.82E-03	2.46E-03	2.22E-03
3		4.65E-04	1.11E-03	1.00E-03
6		4.53E-03	7.47E-03	1.14E-03

The mass of filtrate removed during experiments 1, 2 and 6 is slightly higher when compared to the predicted value. This discrepancy can be correlated to human error to precisely detect dryland and therefore stop the experiment. As reported by Ottoboni et al. (2019)[34], to stop filtration at dryland during a manual experiment done with the biotage unit, the operator needs to close the valve that block the ejection of filtrate manually, taking care that the operator stops the experiment when the liquid level reach the top layer of the sedimented cake. There is a good probability that for these two experiments the operator stopped the filtration experiment when the liquid level slightly overpassed the cake level (case 1 and 4) or a layer of liquid was left on top of the cake (case 2). However, the displacement model provides accurate filtration end point: filtration ends when the free liquid height is equal to zero, corresponding exactly to the cake height.

The same approach to determine the amount of filtrate removed during washing is used for experimental data and simulated values. Instead, to experimentally determine the concentration of dissolved species in the filtrate removed, quantitative HPLC analysis of the filtrate was conducted. The experimental solute concentrations were compared to the simulated mass fraction of solute species removed using pure displacement or diffusion-dispersion washing mechanisms. Overall, the displacement model is not able to predict the composition well enough due to the washing mechanism approach used and its assumptions. In general, the amount of filtrate predicted with the displacement model is comparable with all the experiments for filtration and washing. However, for the displacement model simulation, a consistent discrepancy is observed between experimental and simulated concentration of dissolved species removed during the first washing stage. The displacement washing mechanism assumes a mechanical displacement of the mother liquor from the cake. Pure displacement is rarely achieved in a physical washing process, therefore residual mother liquor is always left in the small cake pores[25]. To get better simulated washing efficiency, in terms of mother liquor and impurity removal, is therefore required to simulate the washing as the combination of displacement, diffusion and dispersion mechanisms[30]. Indeed, the diffusion-dispersion model shows better accuracy in simulating the concentration of solute species (MFA and CBA) removed during washing. On the other hand, the diffusion-dispersion model is not able to predict liquid mass. This is because of the semi-batch operation and holdup specifications used, leading to no outflow of filtrate or accumulation of solids in the vessel, leading to a higher predicted volume of filtrate.

3.4 DESIGN SPACE EXPLORATION

Model optimization activity was done to determine which parameters affect impurity removal during washing. Ottoboni et *al.* (2019)[34] reported that volume and nature of wash solvent used, and the number of washes done affect the capability to remove
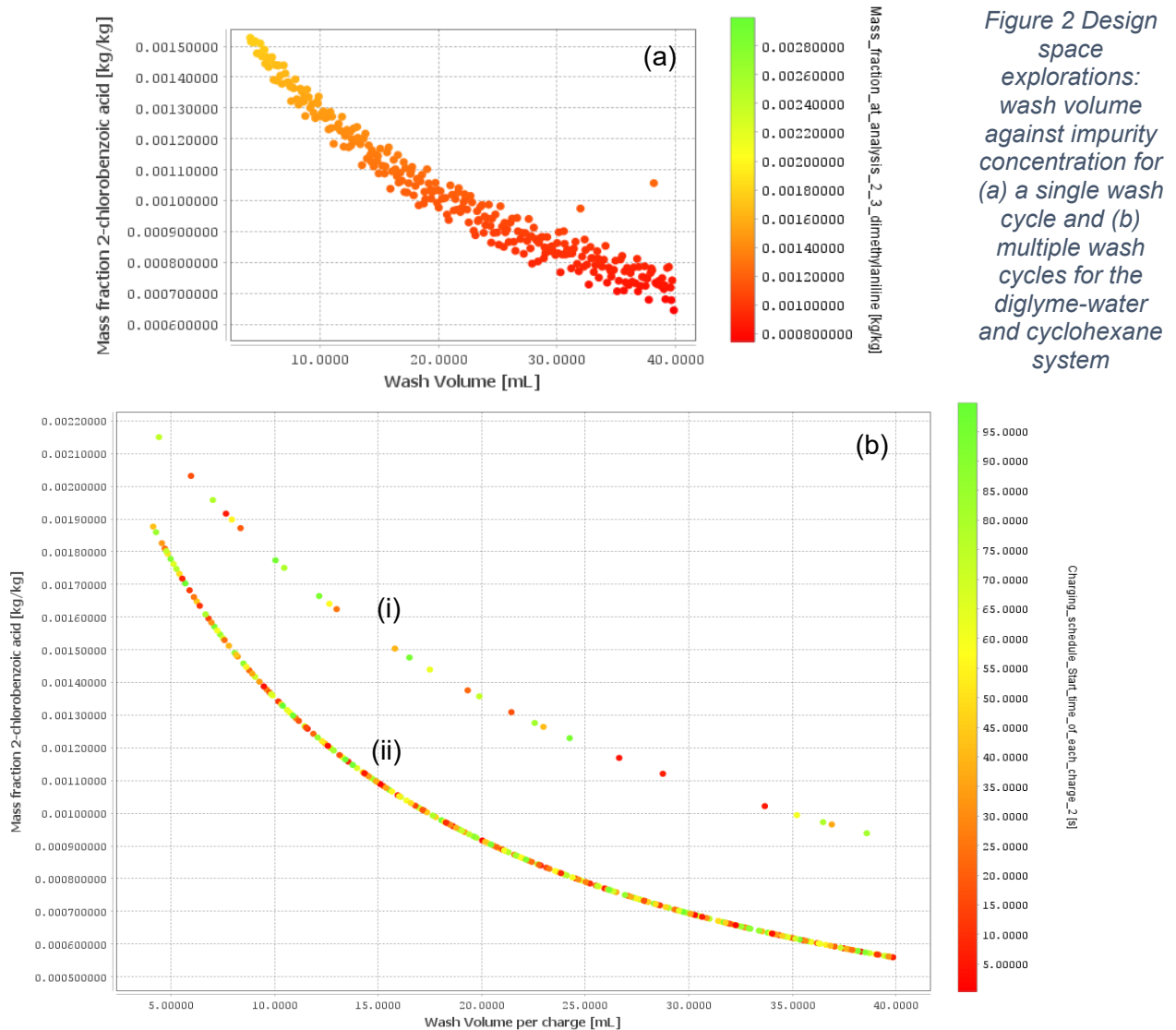

Figure 2 Design space explorations: wash volume against impurity concentration for (a) a single wash cycle and (b) multiple wash cycles for the diglyme-water and cyclohexane system

impurities. Figure 2 below shows the results from the two design space explorations conducted, displaying the wash volume against impurity concentration in both figures for experiment 2. Figure 2(b) shows the effect of multiple washes. It can be seen that when considering a single wash (Figure 2(a)), the more wash solvent you use, the more effective it is at reducing the impurity concentration. This aligns with what would be expected as well. However, the graph also shows that after 20mL (equivalent to 3 cake volumes), the change in impurity concentration is much lower for every mL of wash solvent increase. This is a useful finding as this can be used further for optimization and scalability while reducing solvent usage. Figure 2(b) shows the effect of multiple washes, where 2(b)(i) is two washes and 2(b)(ii) is with three washes. This has been

set up with a fixed volume of 17mL for the first wash, and a varying time and volume for the subsequent washes. The graph suggests that multiple washes do have an effect on the impurity concentration. For the same wash volume, there is a clear reduction in final impurity concentration. It is also quite clear that a higher wash volume leads to a reduction in impurities. The final concentration of the impurity with an additional wash cycle is also similar to the case with only a single wash with a higher wash solvent volume used. Ottoboni et *al.* (2019 and 2020)[34, 44] demonstrated that small and multiple aliquots of wash solvents improve impurity removal, since with multiple washes the back-mixing effect can be minimized respect the use of a single large aliquot of wash solvent. As reported by Ottoboni et *al.*, washing the cake with a single aliquot of wash solvent cause longer contact time between impure mother liquor and clean wash solvent, with risk of impurity migration in the clean wash solvent. Since this model was design to have instant mixing between mother liquor and wash solvent during washing, the model is not able to predict the intermediate or null back-mixing effect, and therefore is not capable to distinguish the impurity removal effect due to different washing cycles described by Ottoboni et *al.*[34, 44].

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 two modelling approach, design to use different washing mechanisms like pure displacement (integrated pressure filter and washing model) or diffusion dispersion (washing model based on MSMPR diffusion-dispersion mixing crystallizer). The filtration and washing data used for the model comparison with the experiments are filtration Darcy plot (volume of filtrate removed versus time) and the solvent mass removed during filtration and the concentration of the mefenamic acid (MFA) and 2,3-chloro benzoic acid (CBA) removed during washing, dissolved in the removed filtrate. Overall, the simulated Darcy's plots reported in Figure 1 reproduce with a good accuracy, except for experiment 6.

Considering the mass of filtrate removed during the experiments, in some cases the predicted outcome is slightly different when compared to the experimental value: the pressure filter model considers a filtration process exactly stopped to dryland, while during the experiments human error in estimating filtration end point can interfere with the accuracy of the results.

Comparing the experimental and predicted composition of filtrate removed during filtration and washing generated with the integrated pressure filter and washing model and the MSMPR model, the pressure filter model is not able to predict the composition well enough due to the washing mechanism approach used (displacement mechanism) and the mechanism assumptions. Instead, to get better simulated washing efficiency, in terms of mother liquor and impurity removal, is therefore required to simulate the washing as the combination of displacement, diffusion and dispersion mechanisms, and therefore the MSMPR washing model is capable with good accuracy to get the final composition of the filtrate after filtration and washing.

The diffusion-dispersion model (MSMPR washing model) was then used to for design space exploration (using the Global Systems Analysis approach) to identify which washing conditions (wash solvent volume, amount of washing stages, and washing time) 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 the wash solvent volume use resulted in a lower amount of residual impurity left in the washed cake. Another outcome obtained from the design space exploration was that there is no difference in final purity between using multiple small aliquots of wash solvent or using one big aliquot of wash solvent to wash the cake. This result, that is contradicting previous investigations[34,44], is due to the assumptions used to design the model.

Future work will be done to consider dissolution of the solid cake, with and without impurities, with considerations for the non-homogeneous composition of the cake during washing, and to consider intermediate or null back-mixing effect occurring during washing.

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