Continuous integrated filtration, washing and drying of aspirin: digital design of a novel intensified unit

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Abstract: Within the recent modernization of pharmaceutical manufacturing, an important milestone consists in developing enabling technologies for end-to-end continuous production of drug products. Continuous filtration, washing and drying of active pharmaceutical ingredients from mother liquors in upstream manufacturing are critical steps for achieving end-to-end continuous production. In this work, we develop a mathematical model for a novel intensified carousel system capable of continuously filtering, washing and drying a slurry stream into a dry crystals cake. The mathematical model consists of detailed dynamic differential mass, energy and momentum balances, capable of tracking the solvents and impurities content in the cake (critical quality attributes) across the entire carousel. We successfully demonstrate the model features by identifying the probabilistic design space in a simulation study for the isolation of aspirin crystals in the carousel, accounting for model uncertainty through Monte Carlo simulations.

Keywords: Continuous pharmaceutical manufacturing, Mechanistic process modeling, Quality by Design, Design space identification, Chemical Process Control

1. INTRODUCTION

Traditional batch pharmaceutical processing is transitioning to a more continuous production mode, due to the general agreement among practitioners and regulatory bodies on the benefits of continuous manufacturing for process efficiency and product consistency (Lee et al., 2015). Continuous active pharmaceutical ingredient (API) purification after the synthesis section represents a key step in the end-to-end continuous paradigm, as impurities not eliminated here will be transferred down to the drug product. API purification is typically achieved through a train of crystallization, filtration, washing and drying steps. Even though many studies have been conducted on continuous crystallization, investigations on continuous implementations of filtration, washing and drying lag behind, and the continuous integration of purification units is even less explored, both experimentally and computationally.

Filtration, washing and drying unit operations should be designed altogether in an integrated fashion with the support of mathematical models, given the strong interaction among their design and operating parameters. Knowledge-based design is critically important in API manufacturing, as emphasized by the recent interest in enhancing pharmaceutical operation through process understanding, promoted by the US Food & Drug Administration (FDA), e.g. through the Quality-by-Design initiative (FDA, 2004). Nonetheless, in the process and pharmaceutical industries solid/liquid separation is still typically conceived through empirical methodologies and shortcut methods, designing each of the processing steps separately (Tarleton and Wakeman, 2006). Early studies on integrated solid/liquid separation design (Wibowo et al., 2001) investigate the effect of the crystal size distribution (CSD) of the crystallizer outlet slurry onto the subsequent purification operations employing short-cut methods. Integrated API isolation is considered within a more advanced modeling framework by Benyiahia et al. (2012). The authors develop a dynamic model of a plant-wide continuous pharmaceutical process, including the isolation section, but their focus is on plant-wide simulation of a specific process, rather than in addressing the current issues in API purification design. Sen et al. (2013) provide useful information on the effect of purification operations onto the properties of the drug product through a flowsheet model, built combining hybrid population balances and discrete element method modeling. However, their flowsheet is a digital assembly of unit operation models, and it does not have a physical counterpart that has actually been used for API purification. As such, fundamental phenomena occurring in real plants are not investigated (for example, the washing step is not included in the flowsheet, and the effect of model uncertainty is not considered). Overall, a comprehensive work on detailed mathematical modeling and knowledge-based design for an actual continuous API filtration, washing and drying process is still missing in the literature.

In this study, we develop a comprehensive mechanistic model of a novel carousel system for integrated continuous filtration and washing (Liu et al., 2019), which has recently been upgraded to include a drying component, too. The unit, manufactured by Alconbury Weston Ltd (UK), represents one of the few technologies available in the market for continuous API crystals isolation. The carousel is made up of multiple cylindrical ports anchored to a main rotating cylindrical body, presenting different processing stations. The crystallization
slurry is loaded into the port aligned with the first station, and is eventually discharged as dry cake after having been processed in all the stations. During operation, the stations work batchwise simultaneously, carrying out filtration, washing or drying. At every fixed time interval, the main body rotates, moving the content of each port to the following station and enabling continuous operation. Due to the rotation mechanism, the residence time in each station is the same, creating an additional challenge for process design and control. Following a quality-by-design approach, we develop a dynamic model for each processing step, and we assemble them together into the carousel model. We use multi-component macroscopic and microscopic mass, energy and momentum balances for this purpose. The developed models are connected to the upstream crystallization with suitable literature relations, linking the physical properties of the filtered cake to the CSD of the crystallization slurry (Yu et al., 1996; Bourcier et al., 2016). The modeling framework is then used for calculating the probabilistic design space (DS) for the isolation of aspirin from an aqueous slurry, in which a non-volatile impurity is also included. The obtained DS meets the objective of integrated design of continuous API purification, as the DS defines the probability of meeting the target critical quality attributes (CQA) of the product for all the explored combinations of critical process parameters (CPP) and feed conditions (critical material attributes, CMA). A risk-based approach (García-Muñoz et al., 2015) is followed for the DS identification, accounting for model uncertainty through Monte Carlo simulations.

The rest of the manuscript is organized as follow. The carousel unit is described in Section 2, while the developed mathematical models are outlined in Section 3. The calculation of the DS for the aspirin case study is presented in Section 4, before of the concluding section.

2. THE CONTINUOUS CAROUSEL

Alconbury Weston Ltd designs and manufactures a wide variety of carousels for continuous filtration, washing and drying. The main difference across the different types of carousels concerns the volume and the overall number of the ports, which can be chosen based on the specific application. In this work we refer to a prototype (Fig. 1) made up of five ports, each with a diameter of 1 cm and maximum capacity of 10 mL, corresponding to five processing stations. All the ports are exposed to atmospheric pressure on the top. The first four stations at the bottom present a filter mesh, connected to a vacuum pump providing the pressure drop ΔP necessary for liquid and gas displacement. The slurry is loaded into the first port, where filtration is carried out. We distinguish between actual filtration, during which a slurry hold-up is still present on top of the forming cake, and cake deliquoring, which occurs after the end of filtration and consist in the mechanical displacement of the liquid retained within the cake pores. After a rotation of the carousel, in the second station a volume of wash solvent is sent on top of the cake, and eventually filtered and (partially) deliquored out. No more liquid is added in the third station, where the cake is only further deliquored. In the fourth station thermal drying is carried out through a flow of hot air. This final step is necessary to achieve the target levels of cake purity before discharge, as, due to capillary forces, there is an equilibrium liquid concentration in the cake that cannot be eliminated through deliquoring. Finally, the dry cake is ejected from the carousel through the action of a pneumatic piston.

Fig. 1. The continuous carousel for integrated filtration, washing and drying. Stations 1-4 present a filter mesh at the bottom, and are connected to the vacuum pump, while station 5 is open for cake discharge.

3. MATHEMATICAL MODELING

3.1 Carousel model overview

The input/output structure of the carousel model is summarized in Fig. 2. Given a set of CMA, CPPs and control variables (CVs), the model predicts the solvent and impurities content in the discharged cake (CQAs). The carousel model also needs the cake physical properties (such as porosity and specific resistance) as inputs. If this information is not available from experimental data, approximate values can be obtained from the slurry CSD exploiting literature models (Section 3.2). The carousel model is obtained assembling together the dynamic models of the four different processes occurring within the unit, namely (i) slurry filtration, (ii) cake deliquoring, (iii) cake washing and (iv) thermal drying. The sequence within which the processing steps occur in the physical unit is a nonlinear function of the inputs, and cannot be determined a priori. For example, a deliquoring step occurs in the first station only if the filtration duration Δt_{filt} for the particular set of inputs is smaller than the set cycle duration Δt_{cycle}. On the other hand, if a very small Δt_{cycle} is set when simulating the filtration of a slurry presenting very low filterability, filtration might end only when the cake has reached, for example, the third station, and washing will not happen in the second station. A logic-based algorithm is implemented within the carousel model to handle this issue and to call the standalone models of the processing steps mimicking the operation of the physical unit.

The models of all the processing steps are developed through differential one-dimensional balances for the reference system in Fig.3. The main assumptions common to all the models are: (i) multiphase system (solid and liquid phases always present, gas phase present in deliquoring and drying), (ii) multicomponent system (formed by the API, one or more solvents, and possibly additional impurities), (iii)
homogeneous, isotropic and constant CSD and cake physical properties, iv) pure solid phase (composed by only the API), v) ideal gas behavior, vi) the liquid phase is an ideal solution, and vii) the set CMAs, CPPs and CVs do not vary during operation. Thermal drying is the only processing step considered not to be isothermal. Beside the relevant CMAs, CPPs, CVs and physical properties, all the models require the initial profiles of cake saturation $S$ (volume of liquid in the pores over total pores volume) and of components concentration in the liquid phase as inputs, and they provide the final values of the same profiles as outputs, which become inputs to the following model. From these profiles, one can calculate and monitor the solvents and impurities content (CQAs) in every point of the cake all across carousel processing. In the following subsections, the models for the cake physical properties and the different processing steps are presented. All the models are implemented and solved in the MATLAB environment. The deliquoring and drying models are coded in C and interfaced with MATLAB through a C-MEX function to speed up the computations.

### 3.2 Cake physical properties models

The physical properties of a size-dispersed cake can be obtained with good approximation from the following literature relations, although experimental measurements are needed for higher accuracy. Expressing the CSD as percentage volume distribution $f(d_p)$, with respect to particle size $d_p$, the cake porosity $\epsilon$ (ratio between pores volume and cake volume) can be predicted by the mixture model developed by Yu et al. (1996), which also factors in the particle shape effect (the model is not reported here for sake of conciseness). The specific cake resistance $\alpha_m$ [m/kg] is given applying a resistance additivity hypothesis to the Kozeny–Carman model (Bourcier et al., 2016), accounting for the contribution of every bin of size $d_p$ in the CSD to the overall resistance to the flow:

$$\alpha_m = \sum f(d_p)1800 \epsilon \left( \frac{1}{\epsilon^2} \right) \phi \frac{1}{\rho_s} \frac{1}{\mu} ,$$

(1)

### 3.3 Filtration model

The solvent and impurity content in the fully saturated cake at the end of filtration are immediately obtained from the initial slurry composition, as during filtration the liquid phase composition does not vary. The significant variables to be calculated with the filtration model are $\Delta P_{\text{cake}}$, the cake height $L_{\text{cake}}$ and the time profile of filtrate volume $V$. The driving force for the process $\Delta P$ is the sum of the pressure drop through the cake $\Delta P_{\text{cake}}$ and the pressure drop through the filter medium $\Delta P_{\text{filter}}$:

$$\Delta P = \Delta P_{\text{cake}}(t) + \Delta P_{\text{filter}}(t)$$

(3)

Making use of the Darcy law (Muskat and Meres, 1936), (3) is rearranged to yield the instantaneous filtrate flowrate:

$$\frac{dV}{dt} = \frac{\alpha_m \mu V_{\text{slurry}}}{\mu + \rho_s} \frac{\Delta P}{d V_{\text{filtration}}}$$

(4)

where $V$ is the filtrate volume, $\mu$ is the liquid viscosity, $A$ is the filter cross-section, $V_{\text{slurry}}$ is the amount of slurry loaded in the port, $c_{\text{slurry}}$ is the initial concentration of crystals in the slurry, $R_m$ is the filter medium resistance and $V_{\text{filtration}}$ is the volume of filtrate at the end of filtration, which from a mass balance is:

$$V_{\text{filtration}} = V_{\text{slurry}} \left( 1 - \frac{c_{\text{slurry}}}{\rho_s} \left( 1 + \epsilon \frac{V}{A} \right) \right)$$

(5)

Under the assumption of constant $\Delta P$, (4) is integrated into the quadratic law expressing $V$ as function of time:

$$\frac{\alpha_m \mu V_{\text{slurry}} c_{\text{slurry}}}{2 A^2} V^2(t) + \frac{R_m}{A} V(t) - \Delta P \int_0^t = 0$$

(6)

From (4), $\Delta P_{\text{filter}}$ is calculated imposing $V$ equal to $V_{\text{filtration}}$:

$$\Delta P_{\text{filter}} = \frac{\alpha_m \mu V_{\text{slurry}} c_{\text{slurry}}}{2 A^2} \Delta P + \frac{\rho_s c_{\text{slurry}} V_{\text{filtration}}}{A \Delta P}$$

(7)
At the end of filtration and during all the subsequent processing steps, \( L_{\text{cake}} \) and \( \Delta P_{\text{cake}} \) correspond to, respectively:

\[
L_{\text{cake}} = \frac{V_{\text{dewater cake}}}{P_b(1+\epsilon d_p)}
\]

(8)

\[
\Delta P_{\text{cake}}(t \geq t_{\text{filt}}) = \Delta P \left( 1 - \frac{r_m}{a_m L_{\text{cake}} p_b(1+\epsilon d_p)} \right)
\]

(9)

### 3.4 Deliquoring model

During deliquoring, the liquid withheld within the pores flows out of the cake, and is replaced by the flowing-in gas phase. The fundamental cake properties for the deliquoring step are the threshold pressure \( P_b \), above which the mechanical displacement of the cake saturation starts, and \( S_{\text{eq}} \), the cake equilibrium saturation for deliquoring. As for the other cake properties, they can be either measured or predicted. While \( P_b \) only depends on the solid physical properties, \( S_{\text{eq}} \) is also affected by \( L_{\text{cake}} \) and \( \Delta P_{\text{cake}} \). Tarleton and Wakeman (2006) found a reliable relation to predict \( P_b \), to which we apply the additivity hypothesis to account for the CSD:

\[
P_b = \sum f(d_p) \frac{4.6(1+\epsilon d_p)}{\epsilon d_p} \sigma,
\]

(10)

where \( \sigma \) is the liquid surface tension. We factor the additivity hypothesis also into the established literature model for \( S_{\text{eq}} \) (Tarleton and Wakeman, 2006):

\[
S_{\text{eq}} = \frac{\sum f(d_p) \frac{0.155}{\epsilon d_p}}{\sum f(d_p) \frac{1}{\epsilon d_p}}
\]

\[
N_{\text{cap}} = \frac{S_{\text{eq}}}{(1-\epsilon d_p)}
\]

(11)

(12)

where \( N_{\text{cap}} \) is the capillary number and \( d_p \) is the liquid density. We use the Darcy law for multiphase flow (Muskat and Meres, 1936) for computing the local liquid velocity \( u_l \):

\[
u_l = \frac{k_{\text{lid}} \Delta P_{\text{cake}}}{P_l \epsilon}
\]

(13)

where \( P_l \) is the local liquid pressure, and the liquid relative cake permeability \( k_{\text{lid}} \) is obtained through (Wakeman, 1979):

\[
k_{\text{lid}} = k_{\text{li}} S_{\text{R}}^{3.5n_l}
\]

(14)

\[
S_{\text{R}} = \frac{S_{\text{avg}} - S_{\text{eq}}}{1 - S_{\text{eq}}}
\]

(15)

In (14-15) the pore size distribution parameter \( \lambda \) is a calibration parameter for the model (usually assumed equal to 5), and \( P_g \) is the local gas pressure. \( P_l \) in (13) is calculated with (15), assuming that the gas pressure gradient is linear and constant, with total gas pressure drop through the cake equal to \( \Delta P_{\text{cake}} \), known from (9). Short-cut methods are usually resorted to in the literature for modeling the time evolution of the average cake saturation during deliquoring, while the liquid composition is assumed constant and uniform. Instead, we develop a detailed partial differential equations (PDEs) system, starting our derivation from Wakeman’s early work (Wakeman, 1979). The differential total mass and species balances respectively read:

\[
\frac{\partial S}{\partial t} = \frac{1}{\epsilon} \frac{\partial q_y}{\partial z},
\]

(16)

\[
\frac{\partial \phi}{\partial t} = -\frac{u_l \phi}{\epsilon} S
\]

(17)

where \( c_{i,L} \) is the local liquid concentration of species, and \( N_l \) is the number of species in the liquid. The model (10-17) presents 1+\( N_l \) PDEs, that we semi-discretize with a high-resolution finite volume method (Van Leer, 1974) along \( z \). The resulting ODEs are integrated with MATLAB’s ode23s solver to yield the dynamic profiles of \( c_{i,L} \) and \( S \) during the process.

### 3.5 Washing model

Cake washing is a step of utmost importance within API isolation, during which the slurry mother liquor is in major part replaced with a wash solvent. Washing is typically carried out for i) reducing the content of impurities (especially the non-volatile ones that cannot be eliminated through thermal drying) and ii) improving the drying performance with a wash solvent more volatile than the mother liquor. At the end of washing, the cake is always fully saturated. During the washing of a non-pre-deliquored cake, dynamic profiles of \( c_{i,L} \) are given by a species mass balance:

\[
\frac{\partial \phi(W, z)}{\partial t} = \frac{c_{i,L}(W, z)}{\phi(W, z)} \frac{\partial (\Delta L_{\text{cake}} \phi(W, z))}{\partial z} + \frac{\partial \phi(W, z)}{\partial z} \frac{\partial (\Delta L_{\text{cake}} \phi(W, z))}{\partial t} + \frac{\partial (\Delta L_{\text{cake}} \phi(W, z))}{\partial z} \phi(W, z) + \phi(W, z) \frac{\partial \Delta L_{\text{cake}}}{\partial t} + \phi(W, z) \frac{\partial \phi(W, z)}{\partial t}
\]

(18)

in which \( \Delta L_{\text{cake}} \) is the axial dispersion coefficient of \( i \), which can be calculated through literature correlations or regressed from experimental data. Short-cut approaches are typically adopted in the literature for computing (18). Differently, we make use of the analytical solution of (18) found by Lapidus and Amundson (1952), reformulated in terms of washing ratio \( W \) (ratio between employed volume of wash solvent and volume of cake pores):

\[
\phi(W, z) = \frac{c_{i,L}(W, z)}{c_{i,L}(W=0, z)} = 0.5 \left[ \text{erfc} \left( \frac{\Delta L_{\text{cake}} W}{2 \sqrt{\Delta W}} \right) \right] + \text{exp} \left( -1.56 \phi(W, z) \right) \cdot \left( -1.72 \phi(W, z) \right)
\]

(19)

For a pre-deliquored cake of average saturation \( S_{\text{avg}} \), we account for the pre-deliquoring effect on washing with a corrected washing ratio \( W_{\text{corr}} \) (Tarleton and Wakeman, 2006):

\[
W_{\text{corr}} = W_{\text{sat}} \cdot \left( 1 - S_{\text{avg}} \right) \exp(-1.56 \phi(W, z = L) - 7.4 \left( 1 - S_{\text{avg}} \right) \exp(-1.72 \phi(W, z = L))
\]

(20)

### 3.6 Thermal drying model

During thermal drying, a flow of hot dry gas is sent onto the cake, to dry it below \( S_{\text{eq}} \). We calculate the local drying rate \( \dot{m}_i^{\text{L-G}} \) [kg/(m$^3$ s)] for species \( i \) as (Burgscheiwer and Tsotsas, 2002):

\[
\dot{m}_i^{\text{L-G}} = h_{\text{M,at}} \cdot a \cdot (P_{\text{sat,at}} - P_g) \eta_i
\]

(21)

where \( h_{\text{M,at}} \) is the mass transfer coefficient (obtained from correlations or experimental data), \( a \) is the cake specific surface, which we calculate as \( a = 6/d_p \) (where \( d_p \) is the Sauter diameter calculated from the CSD), and, for species \( i \), \( P_{\text{sat,at}} \) is the saturation pressure (calculated through Antoine equation), \( P_g \) is the partial pressure, and \( \eta_i \) is a factor accounting for mass transfer limitations, mainly due to capillarity, that occur when the weight content of \( i \) in the cake \( w_i^{\text{cake}} \) becomes lower than...
a critical value \( w^\text{crit}_{\text{cake}} \). We approximate \( \eta_i \) assuming it to be equal to the normalized moisture content:

\[
\eta_i = \begin{cases} 
1 & \text{if } w_i, \text{cake} \leq w^\text{crit}_{\text{cake}} \\
\frac{w_i, \text{cake} - w^\text{crit}_{\text{cake}}}{w^\text{crit}_{\text{cake}} - w^\text{eq}_{\text{cake}}} & \text{if } w_i, \text{cake} > w^\text{crit}_{\text{cake}}
\end{cases} 
\]  

where \( w^q_{\text{cake}} \) is the equilibrium content of \( i \) in the cake. The differential species mass balance in the cake for the solvents and other impurities present in the liquid reads:

\[
\frac{\partial}{\partial t} c_i,\text{cake}^m = - \dot{m}_i^{\text{L} \rightarrow \text{G}}, \quad \text{for } i = 1, \ldots, N_{\text{vol}}
\]  

where \( c_i,\text{cake} \) is the mass concentration of \( i \) in the cake, and \( N_{\text{vol}} \) is the number of volatile species in the liquid. For non-volatile impurities, \( c_i,\text{cake} \) does not vary during drying, hence (23) does not need to be integrated. From \( c_i,\text{cake} \), the local cake saturation is calculated through:

\[
S = \frac{\sum_{i} c_i,\text{cake} \rho_i,\text{L}}{\rho_c}
\]  

where \( \rho_{i,\text{L}} \) is the mass density of pure \( i \) in liquid form. For the \( N_{\text{vol}} \) volatile components of the liquid phase, the species mass balance in the gas phase, in terms of mass fraction \( w_{i,g} \), is:

\[
\rho_g \epsilon (1-S) \dot{w}_{i,g} = \rho_u \dot{w}_{i,g} + \dot{m}_i^{\text{L} \rightarrow \text{G}}, \quad \text{for } i = 1, \ldots, N_{\text{vol}}
\]  

where \( \rho_g \) is the gas density, and the gas velocity \( u_g \) is given by the Darcy law for mono-phase gas flow in a porous medium (Muskat and Meres, 1936). From experimental findings and literature correlations, inter-phase heat transfer is not limiting for the process, hence the differential energy balance for the system is developed assuming local thermal equilibrium among phases:

\[
\left( p_{g,p,n}U_p c_{p,n,\text{L}}(T) + p_{g,p,n}S + p_{g,p,n} \epsilon (1-S) \right) \frac{\partial T}{\partial t} = - \sum_i (\dot{m}_i^{\text{L} \rightarrow \text{G}} - \dot{w}_{i,g} c_{i,g} \rho_{g} - \dot{w}_{i,g} c_{i,g} - \dot{w}_{i,g} \rho_{g} c_{i,g})
\]  

where \( c_{p,n} \) is the solid specific heat, \( c_{p,l} \) is the liquid specific heat, \( c_{p,g} \) is the gas specific heat, \( T \) is the cake temperature and \( \lambda_i \) is the latent heat of vaporization. The model (21-26) presents \( 1+N_{\text{vol}} \) PDEs, that we semi-discretize with a first order upwind scheme. The set gas inlet composition and temperature \( T_{\text{drying}} \) (inputs of the carousel model) are used as boundary conditions for the problem. The resulting ODEs are integrated with MATLAB’s ode15s solver to yield the dynamic profiles of composition and temperature of cake and gas phase during drying.

### 4. ASPIRIN CRYSTALS ISOLATION: DESIGN SPACE INVESTIGATION

Using the carousel model presented in Sections 3, we determine the probabilistic DS (García-Muñoz et al., 2015) for the isolation of aspirin crystals with the carousel prototype described in Section 2. The liquid phase of the crystallization slurry is composed at 95%w by water, and at 5%w by a non-volatile impurity. Ethanol is used for cake washing. The maximum acceptable ethanol and impurity content in the discharged cake is 0.5%, while water content must be below 1%. Given a fixed grid of CPPs and CMAs, for every point we calculate the probability of meeting the CQAs through a Monte Carlo simulation with 500 realizations, sampling each time the uncertain parameters of the model from their probability distributions. The CPPs of the process are identified as \( \Delta_{\text{cycle}} \) and \( V_{\text{slurry}} \), while \( c_{\text{slurry}} \) is the CMA. Extensive simulation activity showed that the CQAs are not significantly affected by major variations of \( W \) and \( D_{\text{ax}},V \), due to the absence of adsorption phenomena, hence they are not considered, respectively, CPPs or uncertain model parameter. A value of \( W \) equal to one is used in all the simulations, while \( D_{\text{ax}} \) is obtained through literature correlations (Tarleton and Wakeman, 2006). \( T_{\text{drying}} \) and \( \Delta P \) are respectively fixed at 70°C and 50 kPa. Six uncertain parameters are identified and considered in the Monte Carlo simulations (probability distributions reported in Table 1). The parameters are all sampled from a normal distribution, except for \( R_n \), which follows a uniform distribution. During carousel operation, \( R_n \) increases due to fouling phenomena. When a threshold level of \( R_n \) is reached (maximum value of the uniform distribution), a cleaning in place procedure is carried out, and \( R_n \) is restored to its original value (minimum value of the uniform distribution). For sake of simplicity, all meshes are assumed to have the same fouling rate. A sample slurry CSD is generated and used to calculate \( c \) and \( a_0 \) (Section 3.2), to which an estimation error of 3% standard deviation is assumed (also accounting for CSD variability). Since during operation \( V_{\text{slurry}} \) and \( c_{\text{slurry}} \) cannot be kept completely fixed, disturbances of standard deviation 3% on their set-points for every grid point are included within the uncertain parameters. The same \( h_{\text{g},i} \) is used for water and ethanol, and a conservative estimation standard deviation of 10% is assumed, given the high variability of mass transfer phenomena. The obtained probabilistic DS is reported in Fig. 4 through two-dimensional contour plots of variable CPPs at constant \( c_{\text{slurry}} \). When \( c_{\text{slurry}} \) increases, the surface of the feasible operative region is reduced. Through a change of variable from \( V_{\text{slurry}} \) to slurry flowrate \( F_{\text{slurry}} = V_{\text{slurry}}/\Delta_{\text{cycle}} \), the contour plots can be used for assessing the feasible operative conditions of maximum throughput.

### 5. CONCLUSIONS

We developed and implemented a comprehensive mathematical model of an intensified and integrated carousel for continuous filtration, washing and drying of crystallization slurries for API isolation. The model has been successfully used for determining the DS for separating aspirin crystals from an aqueous mother liquid, also containing a non-volatile impurity. Model uncertainty was accounted for during DS identification through Monte Carlo sampling from the model parameters probability distributions. Future work will involve using the model for DS identification and process optimization for other slurry systems, upon model calibration with experimental data.

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Table 1. Uncertain parameters for probabilistic DS calculation.

| Cake porosity $\epsilon$ | Unit | Probability Distribution |
|--------------------------|------|-------------------------|
| Filter medium resistance $R_m$ | [1/m] | $\mathcal{U}(3E9, 6E9)$ |
| Mass transfer coefficient $h_m$ | [kg/(m² s bar)] | $\mathcal{N}(0, 9E-4, 6.9E-9)$ |
| Slurry concentration disturbance | [-] | $\mathcal{N}(0, 9E-4 \epsilon_{slurry}^2)$ |

Fig. 4. The calculated robust DS, representing the probability of meeting the target CQAs. In the figures, $\epsilon_{slurry}$ is (a) 100 kg/m³, (b) 150 kg/m³ and (c) 200 kg/m³.

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