Master's Thesis Engineering Technology 2017-2018

Cake washing process development and end point determination based on refractive index

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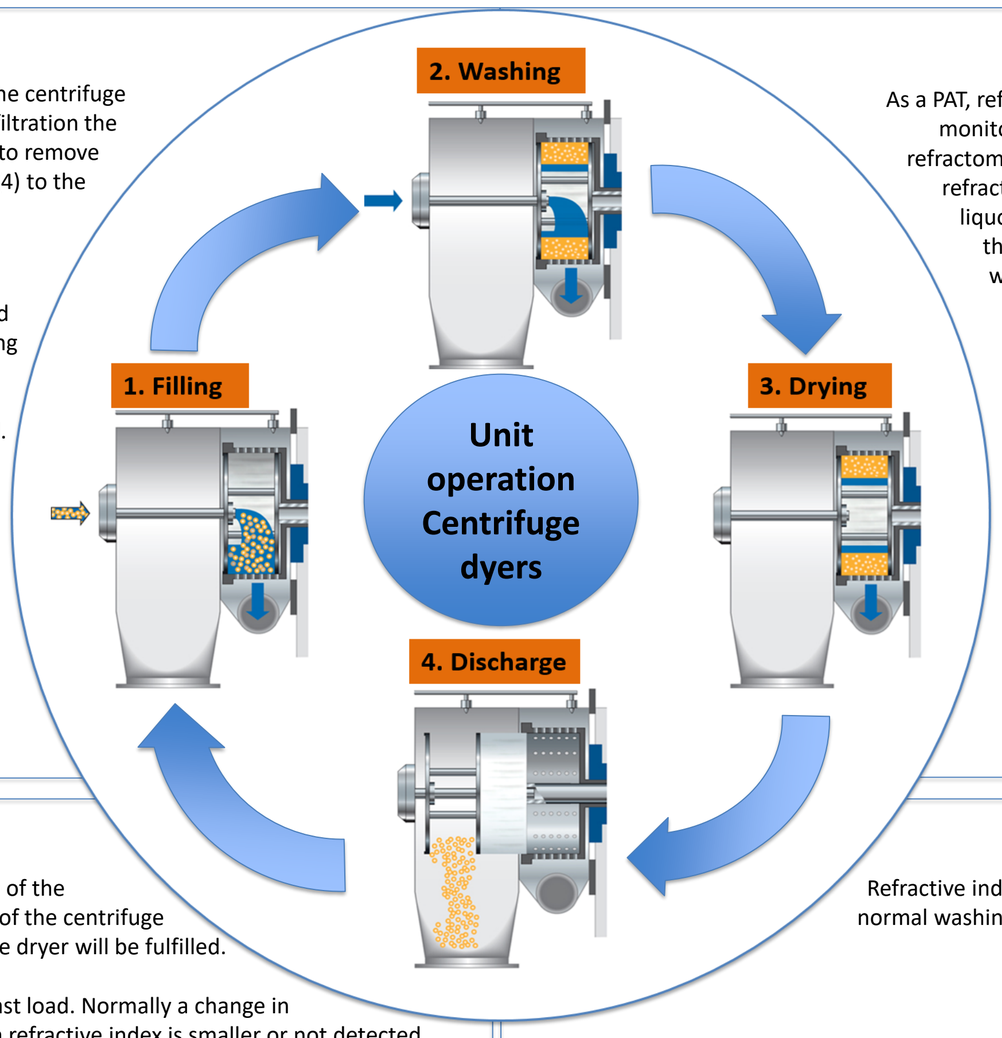
Introduction

The increasing complexity of Active Pharmaceutical Ingredients (API) demands a better understanding of the manufacturing process as costs for development of new products increases. Filtration and drying of the API product frequently become the bottleneck in the production line with production figures of several hundreds of tons per year. Therefore, it is important that filtration and drying characteristics of the API products are examined at an early stage in development.
In industrial applications, the cake washing process step is usually treated as a black box where optimisation is performed through trial and error. Decisive progress has been made in academia by the development of physical models to describe the washing phenomena inside a porous structure such as filter cakes. Although some models have led to a better understanding of the process, experimental efforts are still inevitable for determining optimization strategies. Streamlining the full-scale production system requires a deep understanding of the different process parameters, such as particle morphology, particle distribution, filtration and drying parameters, crystallization type, ….
Process Analytical Technology (PAT) can be successfully implemented in pharmaceutical and biopharmaceutical industries not only to impart quality into the products, but also to prevent out-of-specifications and to improve productivity. The implementation of PAT eliminates the disadvantages of offline measurements, which involve excessive sampling and in most cases the destruction of the samples taken. Detection of deviations and adjustment of the parameters can be done instantaneous. Besides the instant measurement and fast feedback to the process, PAT provides a treasure of process knowledge.
The objective of this project is to improve the washing process by introducing in-line refractive index measurements to determine the end point of the washing step, reducing the washing time and volumes. With the end point determination, the washing step could be standardised and predictive modelling would increase process control. Besides the increased process control, predictive modelling could ease upscaling of the washing process from lab to plant. This study should also clarify whether the refractive index can be used as a tool to detect any deviations, e.g. cake cracking, occurring during washing and more specific how these deviations would show on the refractive index measurement.

Unit operations

The product slurry is filtrated in centrifuge dryers. First the slurry is fed to the centrifuge dryers and excess liquid is removed through centrifugation (1). During this filtration the filter cake is formed. Afterwards, this filter cake is washed (2) and dried (3) to remove impurities. When the filter cake is clean and dry, the product is discharged (4) to the packaging level.



Cake washing

Washing of cakes is an important, often critical, process step that is required during Active Pharmaceutical Ingredient (API) or intermediate manufacturing to achieve the desired product quality and/or improve downstream processing. The main goal of the washing step is to remove any impurities of the cake. During this research, mainly displacement washing will be used.

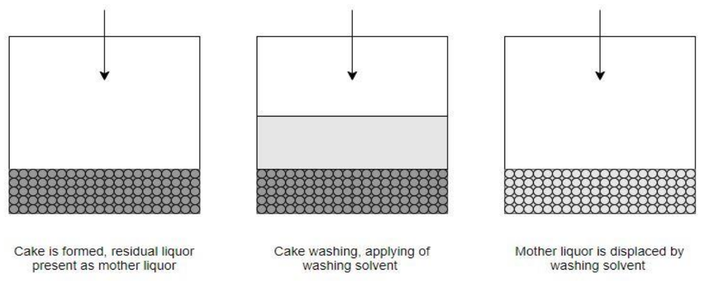


Figure 1 Displacement washing schematic view

Refractive index as PAT

As a PAT, refractive index will be used to monitor the washing process. The refractometer PR-23 will measure the refractive index of passing mother liquor and washing liquid exiting the centrifuge dryer. This data will be used to trend washing curves. These washing curves can be used for End point determination and deviation detection.

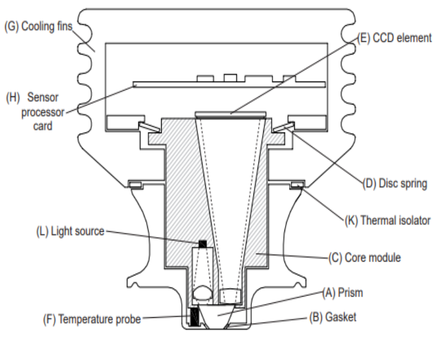


Figure 4 Sensor structure of refractometer PR-23

Advantages	• Instant • Non-destructive
Disadvantages	• No distinction between API and impurities • Requires a lot of process knowledge

Reactor washing

The centrifuge dryer is filled from the reactor vessel in steps, as the volume of the centrifuge dryer is much smaller than this of the reactor vessel. Each filling of the centrifuge dryer is called a load. During each load, the unit operations of the centrifuge dryer will be fulfilled. The process is repeated until the reactor vessel is empty.
The washing trends indicated a big difference between the first loads and last load. Normally a change in refractive index is observed during washing of the filter cake. This change in refractive index is smaller or not detected during the washing of the last load. Instead, when washing a last load, the change in refractive index is observed before the washing commences.

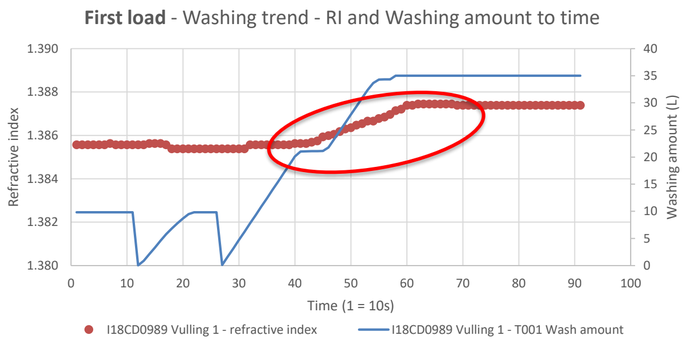


Figure 2 First load washing trend, refractive index and washing amount to time

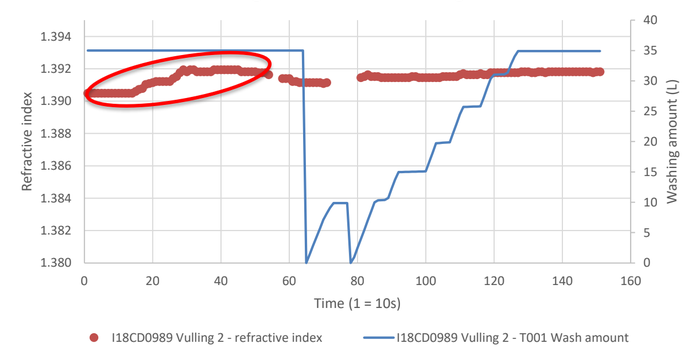


Figure 3 Last load washing trend, refractive index and washing amount to time

The change in refractive index before the washing commences is due to the reactor washing, that is done to clean the reactor vessel from any residual product. The reactor washing is done with the same washing solvent as the normal washing. The amount of washing solvent that is used during the reactor wash is comparable with the amount used during the normal wash. The refractive index indicates that the reactor wash cleans the filter cake from impurities and that no additional washing is needed, as no change in refractive index is observed during washing. *Avoiding washing after reactor wash saves washing solvent and decreases yield loss by solution of the product into the washing solvent, as shown in Table 1.*

Table 1 reactor washing savings

Product	Amount of washing solvent (L)	Cost Reactor wash solvent (€)	Average load size (kg)	Product loss (g)	Yield loss
Alios T3728	43.80	243.59	9.49	35.04	0.37
Alios T3730	52.40	28.14	25.95	120.52	0.46
Alios Crude	268.83	101.39	25.96	510.78	1.97

Deviation detection

Refractive index shows a lot of potential as a deviation detection tool. Deviations to the normal washing procedure, such as change in morphology, higher filling weights, reactor washing, … can be detected using refractive index.

As discussed earlier in reactor washing. During the washing process, an increase in refractive index should be observed, as shown in figure 2.
Using the refractive index, a deviation in batch I18CD0927 was observed, as shown in figure 5. Due to a change in crystal morphology, the washing trends changed in a big way. For batch I180927, with a different crystal structure, no change in refractive index can be detected during the washing. Refractive index measurements would allow for deviation detection during the process, and instant change in process parameters

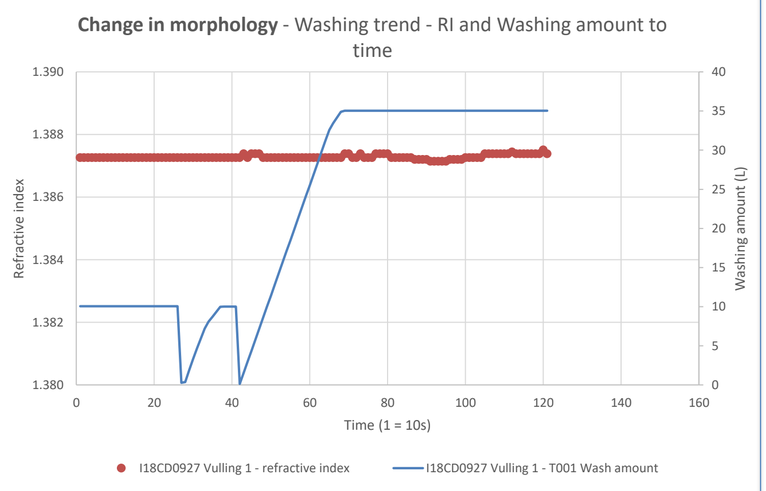


Figure 5 Change in morphology washing trend, refractive index and washing amount to time

Conclusion

Refractive index as a process analytical tool for inline measurements during cake washing poses a lot of advantages. One of the advantages is the accumulation of large amounts of process knowledge on the washing process of each product. Washing curves are very product dependent, which complicates endpoint determination. Further research for a model on endpoint determination will be needed. The refractive index is perfect for deviation detection, due to its high sensitivity. Different deviations, such as crystal morphology, reactor washing and change in solvent ratio, were detected using the refractive index as an analytical tool. Eliminating the normal washing step, when a reactor wash is done, saves up to €243.59 and 1.97% yield loss per batch. The detection of these deviations resulted in a decrease of used washing solvent and a general improvement of the washing process.

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