Gezamenlijke opleiding UHasselt en KU Leuven

2017•2018
Faculteit Industriële ingenieurswetenschappen
master in de industriële wetenschappen: chemie

Masterthesis

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

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Scriptie ingediend tot het behalen van de graad van master in de industriële wetenschappen: chemie

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Preface

I had the opportunity to do my internship and thesis at Janssen Pharmaceutica in Geel. The Chemical Development Pilot Plant is a place where new technology and production processes are developed and optimised. I did my thesis on cake washing process development and end point determination based on refractive index. In this paragraph I would like to thank the people who made this thesis possible.

I would like to thank my promotors Senior Pr. Engineer Steven Rusch and Senior Process Engineer Niels Vandervoort for their guidance. I was always able to ask for help and any questions regarding the research. Niels Vandervoort especially guided me through daily struggles with the data and the development of the new project.

I would also like to thank my internal promotor Prof. dr. ir. Braeken Leen for her help and guidance in the design and structure of my thesis. She helped me to find my way in the large amount of data and results, the form a logical, structural thesis.

The colleagues in the CDPP in Geel were always ready to brighten up the day. They assisted me by helping me to navigate in the large corporal structure of Janssen Pharmaceutica. The production process was taught by the operators, who enthusiastic explained every detail.

Lastly, I would like to thank my parents, my sister and my girlfriend Anke, who supported and motivated me through the internship and my education to industrial engineer.

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Glossary

- Mother solvent/liquor/liquid: the residual liquid that stays trapped in the cake and cake voids after filtration
- Washing solvent/liquor/liquid: the solvent that is used to wash and clean the cake of impurities.
- Deliquoring: dewatering of the filter cake by either sucking or blowing gas through it, or by mechanical force such as squeezing or centrifugal force.
- RI: Refractive index
- WL: Washing liquor
- ML: Mother liquor

Abstract

The goal of the chemical development pilot plant (CDPP) of Janssen Pharmaceutica in Geel is the production of intermediates, process optimisation, scale-up and introduction of new technology in a large plant. The increasing complexity of Active Pharmaceutical Ingredients (API) demands a better understanding of the manufacturing process as costs for development of new products increases. Filter cake washing is a constant bottleneck in the production of new API. Theoretical predictions are hard, due to the strong dependence of the washing on process parameters. The goal of this master thesis is the cake washing process optimisation and endpoint determination based on refractive index.

Cake washing is executed in centrifuge dryers in this study. Refractometers are used to measure the cake washing, whereafter washing curves will be drafted. Washing curves will be used for deviation detection, endpoint determination and process optimisation.

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. The detection of these deviations resulted in a decrease of used washing solvent.

Abstract (Dutch)

Het doel van de *chemical development pilot plant* (CDPP) van Janssen pharmaceutica in Geel is de productie van intermediairen, processoptimalisatie, opschaling en introductie van nieuwe technologie op grote schaal. Door stijgende ontwikkelings- en productiekosten in combinatie met de groeiende complexiteit van actieve componenten in geneesmiddelen, is er een grote vraag voor procesoptimalisatie. Filterkoek wassen is steeds een knelpunt in de productie van geneesmiddelen. Theoretische voorspellingen zijn moeilijk, aangezien het wasproces afhankelijk is van veel parameters. Deze masterproef heeft als doel op basis van brekingsindex het filterkoek wassen te optimaliseren en een eindpuntsbepaling uit te voeren.

Het wassen van de filterkoek wordt in dit onderzoek uitgevoerd in centrifugedrogers. Brekingsindexmeters zullen het wasgedrag van de filterkoek opmeten, waarna wascurves opgesteld worden. Wascurves worden gebruikt voor detectie op afwijkingen, eindpuntsbepalingen en processoptimalisatie.

Wascurves zijn zeer productafhankelijk, wat eindpuntsbepaling moeilijk maakt. Verder onderzoek naar een model voor eindpuntsbepaling is nodig. De grote gevoeligheid van brekingsindex maakt het een perfect analystoestel voor detectie van afwijkingen in het proces. Verschillende afwijkingen zoals verschil in kristalstructuur, reactor wassen en veranderingen in solventverhouding, werden gedetecteerd met brekingsindex. De detectie van afwijkingen resulteerde in een vermindering van het gebruikte wassolvent.

1. Introduction

Johnson & Johnson is an American multinational company founded in 1886, manufacturing medical devices, pharmaceuticals and consumer packaged goods. The headquarter is located in New Brunswick, New Jersey. The company includes 250 subsidiary companies with operations in 60 countries, selling products in over 175 countries. During 2015 Johnson & Johnson had worldwide sales of $70.1 billion. [1]

Janssen in Europe, the Middle East & Africa (EMEA) has activities in more than 100 countries and local offices in more than 30 countries. The region has more than 14,000 employees and R&D investments of more than €1.5 billion annually. There are 7 R&D centers; Beerse (Belgium), High Wycombe (UK), Leiden (Janssen Biologics, The Netherlands), Val-de-Reuil (France), Schaffhausen and Bern (Janssen Vaccines AG, Switzerland) and in Toledo (Spain). There are also 8 manufacturing sites for worldwide distribution of medicines and vaccines in; Belgium (Beerse, Geel and Olen), Ireland (Cork), Italy (Latina), The Netherlands (Leiden) and two in Switzerland (Schaffhausen and Bern). [2] A couple of the most well-known medicines produced by Janssen Pharmaceutica are: Imodium, Motilium, Reminyl, …

More specific, this master thesis is performed at the Chemical Development Pilot Plant or CDPP plant at the production site in Geel. In the CDPP plant, research on process scale up from lab to full production is done and production of smaller quantities of products that are still within the testing phases. It consists out of 5 levels Level 4 of the CDPP plant or Solvents and reagents is where all the solvent pipes arrive on the plant. On this level containers can be connected to different solvent pipes that run throughout the whole plant. On level 3 there are 6 big reactor vessels of around 1600 l used for different reactions. The reactors are equipped with a wide range of analysis equipment and different coatings to manage a broad range of products and solvents. Level 2 consists of 3 crystallization reactors (1600 l) where usually crystallization reactions of the desired product will occur. From level 2 the slurry with product and sample are sent to the centrifuge dryers (CD) on level 1. In the CD the desired product is separated from the mother liquor using a centrifuge filter. When needed it is possible to wash and dry the product in these centrifuge dryers. The final product is ejected from the CD to level 0 where it is packed in sealed bags. Beside the 5 levels of the CDPP there are 2 modules: module A and module B. Module A is used for production of end products and hazard products such as fentanyl. Module B is mostly used for production of intermediates and hazardless chemicals. In this project the use of module A will not be further discussed.

1.1. Problem statement

1.1.1. Development of an Active Pharmaceutical Ingredient

The increasing complexity of Active Pharmaceutical Ingredients (API) demands a better understanding of the manufacturing process as costs for development of new products increases, while patent life is fixed. In recent years, pharmaceutical firms have faced mounting pressure to reduce ever-increasing R&D as well as production costs. The commercialisation of new drug can require up to $1.8 billion in total per product, a high cost which has been steadily increasing. [3] Generic drug manufacturers also increase the pressure on pharmaceutical firms as patent life of the products stay fixed. [4] Considering clinical approval and patent duration, by the time the product reaches the market half of its patent life may have expired; once this occurs, the original developer may lose up to 90% of market share to generic manufacturers. [5]

Development of an Active Pharmaceutical Ingredient (API) not only includes pharmaceutical development where the active drug substance is formulated but also the chemical development of the manufacturing final process steps of the API. There are two obvious ways of increasing profit are:

1) More rapid pharmaceutical development and shortening the total time spend on research, thus increasing the time between product release and patent expiration.
2) Streamlining the full-scale production system to reduce production costs, such that traditional research-based drug manufacturers can also compete with generic drug manufactures when the patent of a drug has expired. [6]

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, … that will influence the production process. As well as possible bottlenecks inside the manufacturing processes and how these can be solved.

Commonly crystallization is used as a separation and purification technique of the intermediate or final product. In this process, the relevant powder properties of the drug substance are defined that are fundamental for the pharmaceutical formulation process. [7]

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. [7] Therefore, it is important that filtration and drying characteristics of the API products are examined at an early stage in development.

1.1.2. 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. After solid-liquid separation of the API or intermediate product, the mother liquor from the suspension (API / intermediate) remains entrained in the filter cake voids with the extent of saturation being determined by the applied filtration pressure centrifugal G-force.

The terms washing liquor and washing solvent are both commonly used to describe the clean liquid used to wash the cake and remove the residual liquor (mother liquor) inside the cake. The term mother liquor is used for the residual liquor inside the cake after formation of the cake inside the centrifuge dryer. The residual liquor (mother liquor) is usually removed by one of three methods: displacement washing, counter current washing and reslurry washing. Displacement washing will be focussed upon, as this is used during this research.

1.2. Objective

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 the washing process from lab to plant. It would allow prediction of washing volume based on lab tests after verification with the refractive index measurements and dynamically monitor the washing process during operations.

To achieve this goal the influence of washing and cake parameters as e.g., washing liquid temperature, stirring speed (rpm) of the centrifuge and cake thickness on the cake deliquoring and washing on one hand and on the RI measurement or shift in RI value on the other hand have to be investigated. Selection of the relevant parameters will be based on best practices and literature. 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.

2. Literature study

2.1. Development of an Active Pharmaceutical Ingredient

The increasing complexity of API demands a better understanding of the manufacturing process as costs for development of new products increases, while patent life is fixed. In recent years, pharmaceutical firms have faced mounting pressure to reduce ever-increasing R&D as well as production costs. The commercialisation of new drug can require up to $1.8 billion in total per product, a high cost which has been steadily increasing [3]. Generic drug manufacturers also increase the pressure on pharmaceutical firms as patent life of the products stay fixed [4]. Considering clinical approval and patent duration, by the time the product reaches the market half of its patent life may have expired; once this occurs, the original developer may lose up to 90% of market share to generic manufacturers [5].

Development of an Active Pharmaceutical Ingredient (API) not only includes pharmaceutical development where the active drug substance is formulated but also the chemical development of the manufacturing final process steps of the API as shown in Figure 1. Figure 2 shows the multiple manufacturing steps needed, from raw materials to final drug product, for production of a new drug. Considering this typical development cycle of a drug, two obvious ways of increasing profit are:

(1) more rapid pharmaceutical development and shortening the total time spend on research, thus increasing the time between product release and patent expiration;
(2) streamlining the full-scale production system to reduce production costs, such that traditional research-based drug manufacturers can also compete with generic drug manufactures when the patent of a drug has expired [6].

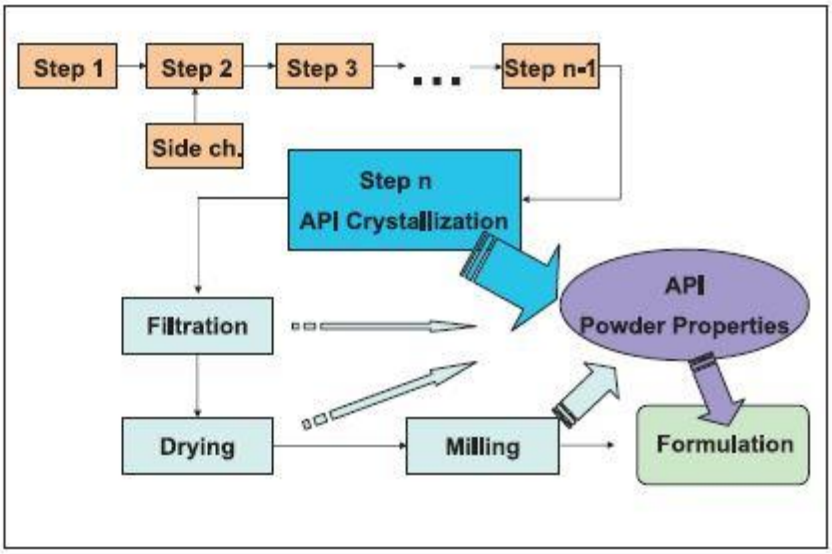

Figure 1 API manufacturing flowchart [7]

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, … that will influence the production process. As well as possible bottlenecks inside the manufacturing processes and how these can be solved. Besides the pharmaceutical development of the new drug, chemical development of the manufacturing process should also be research at an early stage in development to increase the efficiency of streamlining the full-scale production.

Figure 2 shows the synthesis of an API requiring multiple reaction steps with separation of the intermediate from its impurities. Commonly batch cooling crystallization is used as a separation and purification step in pharmaceutical industry, as it is easy to operate, less energy intensive, can achieve high purity in a single step, etc. During synthesis, the relevant powder properties of the drug substance fundamental for the pharmaceutical formulation process are defined [7]. Although the crystallization provides several advantages to other separation and purification processes, batch-to-batch variations are commonly observed. These variations have a large impact on the product properties. This could influence the manufacturing processes downstream of the crystallization [8].

In big production companies, API’s are produced in large quantities of several hundreds of tons per year. Filtration and drying of the API product frequently become the bottleneck in these production lines [7]. Therefore, it is important that filtration and drying characteristics of the API products are examined at an early stage in development. Beside causing bottlenecks for the manufacturing process, filtration and drying could influence the powder properties of the API through abrasion as shown in Figure 2. The extent of this effect should always be taken into considerations when developing the manufacturing process.

Reproducibility in API production is one of the most important features as batch to batch variation are common in large scale installations and could induce a difference in API properties or increase impurity levels in intermediates or the final product. Hence the importance of chemical development of the manufacturing of the API and the design of a robust manufacturing process that yields the desired characteristics at all times.

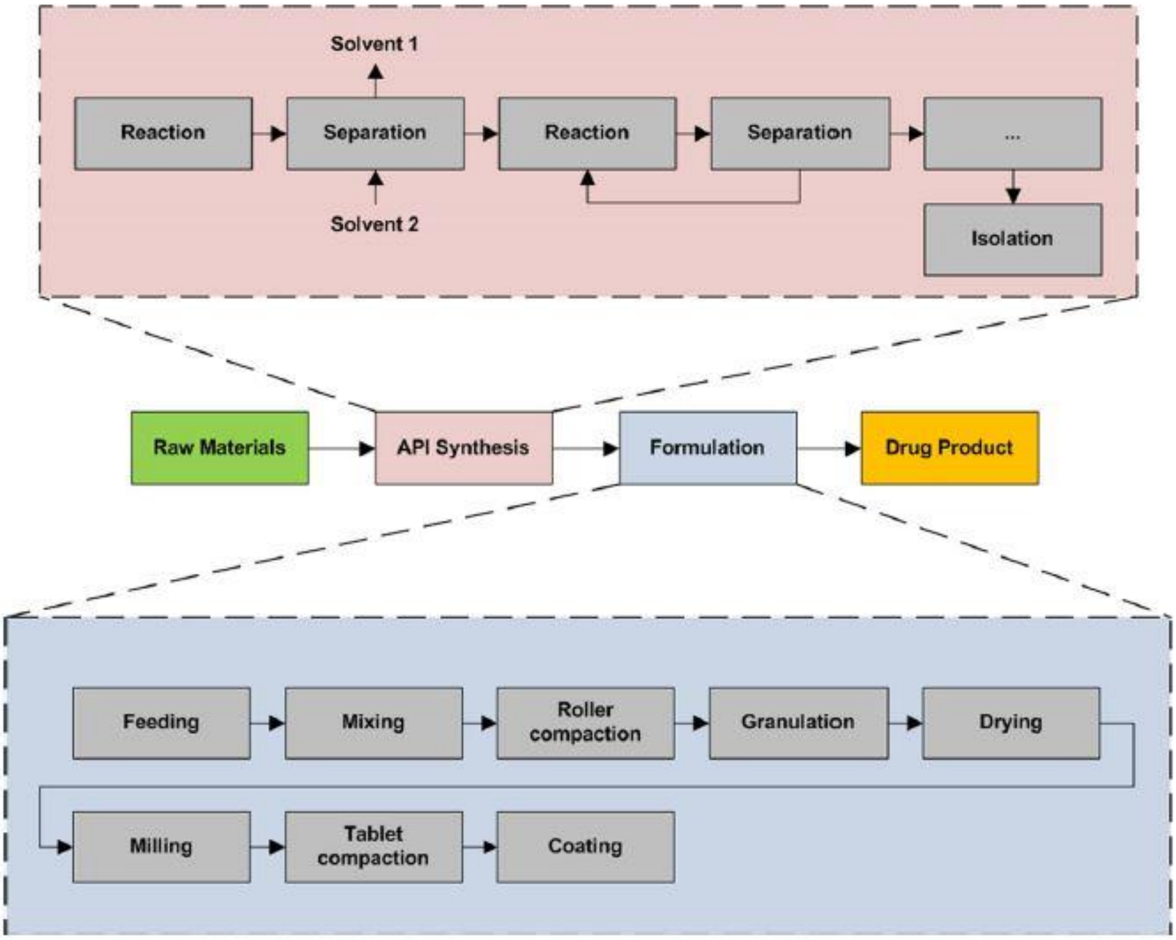

Figure 2 Flowsheet for a pharmaceutical manufarcturing process [6]

This paper will not examine the manufacturing process of an API as a whole, but aims at understanding the filtration and washing process steps of the production of intermediates.

2.2. Cake deliquoring

2.2.1. Irreducible saturation

Cake deliquoring is applied to the dewatering of the filter cake by either sucking or blowing gas through it, or by mechanical force such as squeezing or centrifugal force. The terms deliquoring, dewatering and desaturation are used to describe the removal of solvents and liquids from the solid filter cake and will be used interchangeably in this chapter.

Two important properties of a cake are the threshold pressure and the irreducible saturation. The threshold pressure of a filter cake is the minimum pressure difference needed for any deliquoring to occur. This minimum pressure difference is only used in pressure or vacuum filtration, when using mechanical squeezing or centrifugal filtration this minimum pressure difference is defined as the threshold force.

The irreducible saturation is the lowest saturation of a filter cake that can be achieved at a given pressure with infinite desaturation time without irreversibly deforming the cake. The irreducible saturation is hard to predict or calculate and is best measured with lab tests [9].

The irreducible saturation can be measured using the set up shown in Figure 3. The cake depth and volume of the drained filtrate are recorded. By measuring the driving force across the cake and combining this data with the collected liquid volume of the filter cake, a capillary pressure curve is obtained.

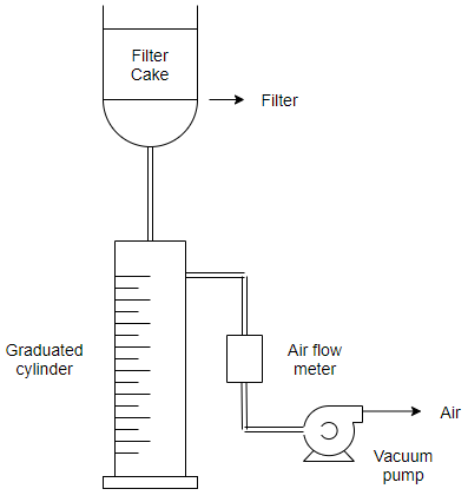

Figure 3 Setup for measuring threshold pressure and capillary pressure curves

Since compressible cakes change heavily in bulk volume, the cake depth must be measured at each driving force. These cakes may remain almost saturated by changing their bulk volume. The cake saturation is calculated from equation (2.1).

$$S = \frac{Volume\ of\ liquid\ in\ the\ cake}{\varepsilon_{av}\ AL} \tag{2.1}$$

In (2.1) AL is the bulk volume of the cake and ε_{av} is its average prosity, which is calculated from (2.2).

$$\varepsilon_{av} = 1 - \frac{W}{AL\ \rho_s} \tag{2.2}$$

where W is the dry weight of solids in the cake and ρ_s is the density of the solids in the filter cake. An example of a complete capillary pressure curve is given in Figure 4.

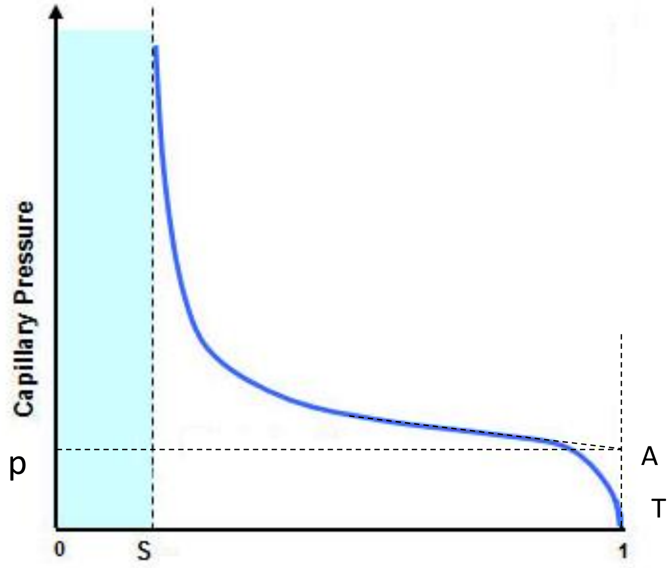

Figure 4 Capillary pressure curve

The final saturation value is the point where no further liquid content removal from the cake is possible. This is the irreducible or infinite saturation ($S_{irreducible}, S_{\infty}$). The minimum pressure that is required for any deliquoring to occur is the threshold pressure, indicated by point T in Figure 4 . Since point T is often hard to identify, a modified point A is chosen. Point A is the intercept of the line at S = 1 and the tangent of the main curve, as shown in Figure 4. The threshold pressure given by point A is always slightly larger than the pressure given by point T. The threshold pressure can also be calculated using equation (2.3):

$$p_b = \frac{4.6\,(1-\varepsilon_{av})\sigma}{\varepsilon_{av}\;x} \tag{2.3}$$

In (2.3) p_b is the threshold pressure, x is the main particle size and σ is the liquid tension.

2.2.2. Capillary pressure

An important parameter in cake deliquoring is the capillary pressure of the filter cake. The capillary pressure determines the irreducible saturation that can be reached of a filter cake, which can be measured in a lab test. However, a lot of cake parameters such as cake resistance, cake thickness, cake compressibility, crystal morphology, … influence this capillary pressure, which makes it hard to predict the irreducible saturation using the capillary pressure. Besides the irreducible saturation, in combination with the cake resistance, the capillary pressure also influences the desaturation kinetics of a filter cake. [10]

When high pressure difference is used in a technique such as gas displacement deliquoring, extra attention must be payed towards the control of the filter cake at the end of the dewatering process. Especially fine particles have a strong tendency for cracking. [10] In gas displacement deliquoring the fluids in the filter cake are replaced by the passing gas, introducing a high chance of cake cracking. The liquid in the pores are replaced by compressible gas and gas-liquid interfaces are being set up in the pores. These interfaces introduce additional interparticle stresses, the magnitude of which depend largely on the saturation moisture content of the cake. The distribution of these interfaces at the microscopic level manifest themselves at the macroscopic level as cracks in the filter cake, sometimes also accompanied by cake shrinkage. [9]

Any flowing liquid or gas will preferentially follow the crack in the filter cake rather than going through the whole filter cake. If cracking occurs when using the gas displacement method before the irreducible, or required, saturation is reached, any further deliquoring of the filter cake will not be effective. The gas will flow through the crack and will not displace any residual liquid inside the cake. When using the centrifugal filtration deliquoring method, deliquoring of the cake can continue as the centrifugal force is not influenced by cake cracking. However, any formed cracks in the filter cake must be sealed before proceeding with washing step. Proceeding with washing of a cracked cake will result in bad cake washing and yield loss, as the washing liquid will preferentially flow through the crack.

2.2.3. Irreducible saturation of centrifuge cakes

As discussed earlier the irreducible saturation is the lowest saturation that can be reached when deliquoring a cake. When using the centrifugal filtration method, the filter cake is spun in a centrifuge, deliquoring the cake as a result of the centrifugal forces. In pressure or vacuum filtration there is a minimum pressure difference needed for any deliquoring to occur. Whereas in centrifugal filtration a minimum centrifugal force or rotational speed has to be applied on the filter cake. This minimum rotational speed is in all practical cases very low and estimation of this value is not necessary. For centrifugal deliquoring, the irreducible saturation is represented in the equations (2.4) (2.5) [9]:

$$S_\infty = 0.0524\, N_{cap}^{-0.19}\ for\ 10^{-5} \le N_{cap} \le 0.14 \tag{2.4}$$

$$S_\infty = 0.0139\, N_{cap}^{-0.86}\ for\ 0.14 \le N_{cap} \le 10 \tag{2.5}$$

With the capillary number N_{cap} expresses the ratio of the dewatering forces to the surface tension forces retaining the liquid in the cake. N_{cap} is further defined in equation (2.6):

$$N_{cap} = \frac{\varepsilon_{av}^2\, x^2\, \rho_l\, N^2\, r}{(1-\varepsilon_{av})^2 \sigma} \tag{2.6}$$

In this capillary number r is the radius of rotation of the mid-point through the cake thickness. A sharp break in the correlation is noticeable when the ratio of the drainage force to the retentive forces is about 0.14; this probably coincides with a predominance of liquid being held in a pendular state (a state in which liquid is held around the point of contact of the particles) in the pores of a cake.

This phenomenon is also known as liquor load in the centrifuge filter. This may also be interpreted as a breakdown of continuity in a majority of the liquid films throughout the cake voids.

2.3. Cake washing

Washing of cakes is an important, often critical, process step that is required during Active Pharmaceutical Ingredient (API) and intermediate manufacturing to achieve the desired product quality and improve downstream processing. The main goal of the washing step is to remove any impurities of the cake. After solid-liquid separation of the API or intermediate product, the mother liquor from the suspension (API or intermediate) remains entrained in the filter cake voids with the extent of saturation being determined by the applied filtration pressure or centrifugal G-force and the cake capillary pressure (which is a function of the solvent used and the macroscopic cake structure). [11]

The terms washing liquor and washing solvent are both commonly used to describe the clean liquid used to wash the cake and remove the residual liquor (mother liquor) inside the cake. The term mother liquor is used for the residual liquor inside the cake after formation of the cake inside the centrifuge dryer. The residual liquor (mother liquor) is usually removed by one of three methods, which are further explained in 2.3.1, 2.3.2 and 2.3.3.

2.3.1. Displacement washing

Displacement washing is defined as wash liquor passing through the cake once and displacing the mother liquor as shown in Figure 5.

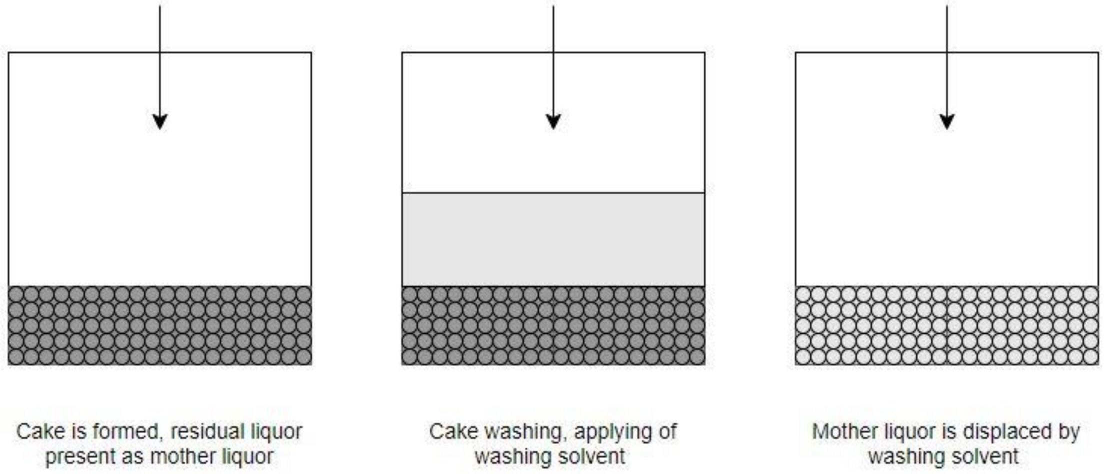

Figure 5 Displacement washing

The displacement process allows only a limited time of contact between the mother and wash liquor during the liquid movement through a filter cake. The purification effect is achieved through the displacement of the mother liquor by the penetrating wash liquor. [12] Ideally the amount of washing liquid needed is the amount of mother liquor still entrained in the cake after cake formation. This ideal displacement of the residual washing liquor, can only be achieved if the used washing solvent is not miscible in the mother liquor. Using an immiscible washing solvent, the chance of axial diffusion and mixing between mother liquor and washing solvent is decreased, increasing the effectiveness of the displacement.

An advantage of displacement washing is the low contact time (residence time) between solvent and cake, causing yield loss by resolving of the product in the washing solvent to be small. However, low contact times could be negative to the end purity of the product as solid impurities don’t have the time to dissolve in the washing solvent. Important in displacement washing is the equal distribution of the washing solvent on the cake. In case of low precipitated impurities on the filter cake or all impurities dissolved in the mother liquor, displacement washing should be focussed.

2.3.1.1. Dilution washing

Dilution washing uses the same principle as (2.3.1) Displacement washing. The only differences between the 2 methods is the miscibility of the washing solvent opposed to the mother liquor. In displacement washing the used washing liquor should is immiscible with the residual mother liquor in the cake, to ensure an efficient displacement. On the contrary, in dilution washing, the washing liquid is miscible in the residual mother liquor. The residual mother liquor, saturated in product and impurities, is diluted by the passing washing liquid. The increased mixing between mother liquor and washing liquor causes more axial diffusion of the washing liquor. Because of the increased axial diffusion and increased mixing, perfect displacement of the mother liquor will not be achieved.

2.3.2. Counter current washing

Counter current washing is a method where all or part of the wash liquor (sometimes mixed with filtrate) emanating from a downstream section of cake is passed through a section of the cake farther upstream as shown in Figure 6.

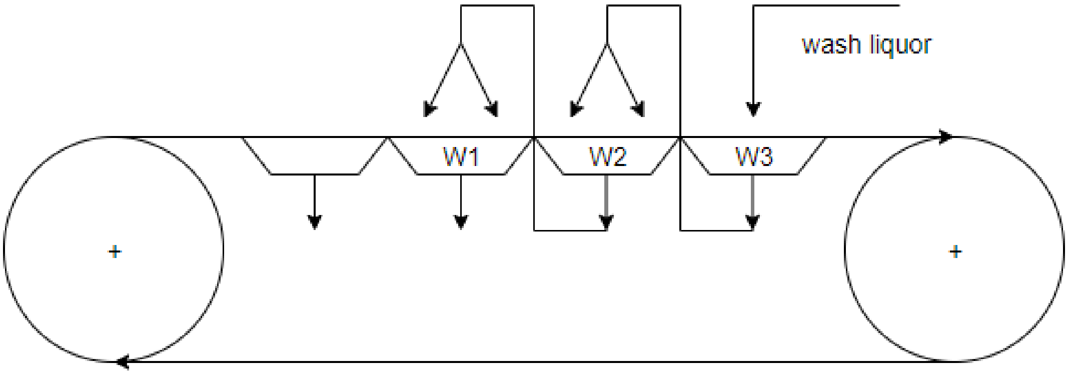

Figure 6 Countercurrent washing on belt filter with three washing zones (W1, W2and W3)

Figure 6 shows a belt filter filtration washing system which is an application of the counter current washing method. Counter current washing is mostly used in continuous washing installations with multiple filters. The advantage of counter current washing is the multiple use of washing liquor. The washing liquor is reused by passing the filtrate through a washing zone farther upstream. This recycling of the washing liquor decreases the amount of washing liquor needed in the process. Because of contamination and use of different products in the pharmacy counter current washing would not be possible.

2.3.3. Reslurry washing

Reslurry washing is a method where the cake is discharged from the filter and then mixed with wash liquid in a separate vessel before being filtered again as shown in Figure 7.

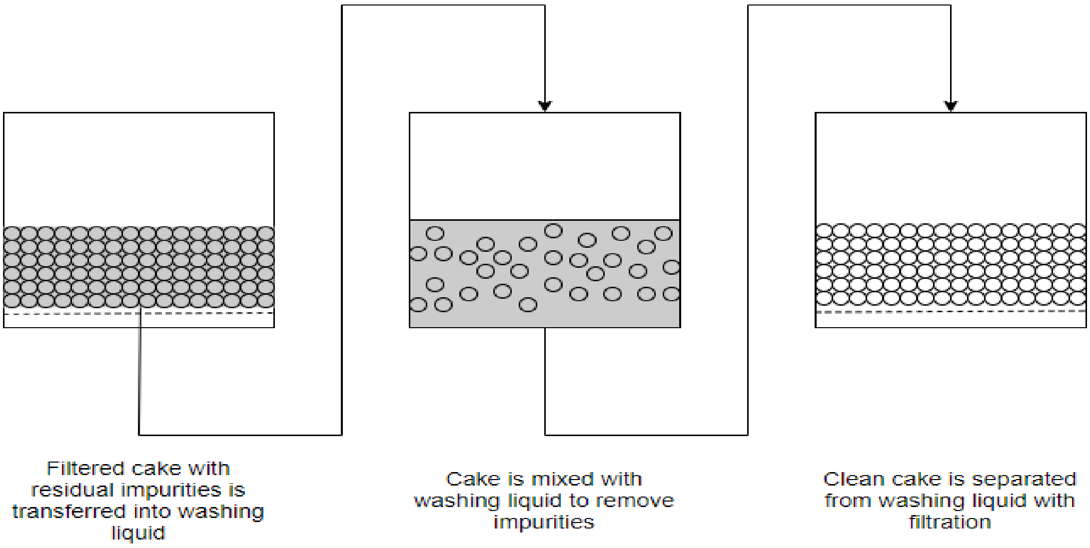

Figure 7 Reslurry washing

Sometimes this whole operation can be carried out on the filter too. Reslurry washing is mostly used for dissolving solid impurities in the cake. Using the reslurry washing method, large amounts of washing liquids and contact time between product and washing liquid would be necessary as mass exchange occurs by agitation. The increased contact time between the product and washing liquid, and the large amounts of washing liquid used, will increase the yield loss through resolving of the product into the washing liquid. In contrast, displacement washing only needs a fraction of the amount of washing liquid and contact time needed to reslurry the cake. The big advantage of the reslurry washing method is the end purity of the product. Solid impurities in the cake will dissolve into the washing solvent causing only traces to be left in the cake after washing.

2.3.4. Cake washing predictions

Cake washing in industrial applications is a process step that is usually treated as a black box, where optimization of the process is done through best practices and trial and error. The large number of influencing parameters, possible processes, process combinations and nonideal effect, as well as the complex properties and effects in disperse particulate systems make the correct choice of the washing strategy and process difficult and elaborate. [13] Significant progress on physical models, that describe the washing properties, have been made, but experimental tests are still inevitable for determining optimization strategies. [12]

Although these experimental tests are expensive and time consuming, there is a large need for optimization of the washing process, as this is often the bottleneck in the process chain of the product.

2.3.5. Purpose of cake washing

The purpose of cake washing will be further discussed in 2.3.5.1, 2.3.5.2, 2.3.5.3, 2.3.5.4 and 2.3.5.5. [11]

2.3.5.1. Dissolved impurities removal

Dissolved impurity removal by cake washing requires that the impurities are soluble in the washing liquid and that no anti-solvent precipitation of the impurities occurs as the washing liquids passes through the cake. The desired product should have a low or no solubility in the washing liquid to prevent yield loss during washing. Low dissolution rates are undesired, as they cause increased residence time of the washing liquid in the cake. Instead high dissolution rates for impurities are preferable as contact time and product loss by resolving is decreased. The solubility of solid particles is determined by the interactions between solids and liquids in interfacial areas in relation to the strength of interactions of the bonding force between molecules, atoms, or ions inside each phase. [14] The first used washing solvent should therefore have a composition that matches the mother liquor. If the product has a high solubility in the mother liquor, change of solvent mixture is advised to minimise product loss. When the amount of washing liquid used is fixed and measured during lab testing, extra attention should be paid to the selection of the washing liquid with the right solubility parameters. The selection of washing solvent is discussed in 2.3.7.

2.3.5.2. Solvent displacement for solution phase product recovery

Instead of crystallization of the product, the impurities can also be separated using crystallization. The product rich mother liquor is then displaced using a washing liquid. To prevent product loss by crystallization, the washing liquid should have the same composition as the mother liquor to ensure the solubility of the product. The undesired solid and impurities are typically formed as an insoluble by-product for which limited effort has placed on controlling the precipitation process. This can influence the efficiency of the washing step by, for example, increasing the time spend washing and batch to batch variations. Therefore, crystallization of the undesired product should be robust by controlling dosing and mixing rates.

2.3.5.3. Solvent displacement for downstream process improvement

The use of multiple washing solvent is possible for downstream processing. The displacement of the first washing liquid may be necessary if the drying performance of the wet cake is found to be poor. By using a final washing liquid with different physical properties, such as a low boiling point and higher vapour pressure, downstream processes such as drying can be improved. If the final washing liquid is changed in function of the drying process, the parameters used for the drying process should also be re-assessed, as rapid drying could lead to agglomeration. Viscosity of the second washing liquid should also be considered, as it influences cake washing. Washing solvent with a low viscosity will have a higher tendency to flow through the cake in a stochastic manner, and thus lowering the efficiency of the displacement wash.

2.3.5.4. Solid removal

Solid impurities can be removed using displacement cake washing or dilution cake washing (reslurry washing). In displacement washing the solids are dissolved in the passing washing liquid, and no extra filtration step is necessary. While in reslurry washing the impurities are dissolved during the reslurry process of the cake and the cake needs to be filtrated after this process. These used washing methods are only effective if the solid impurities are soluble in the used washing solvent. Removal of solid impurities using this method should be avoided. Instead the solid impurities should be removed upstream, using e.g. extraction. Dilution washing is unfavourable because of the large amounts of washing liquid needed to reslurry the cake and the time needed to complete this process. Similarly, displacement washing will require a large amount of washing solvent to pass through the cake to enhance the dissolving of the solid impurities in the passing washing liquor. This dissolvement of solid impurities in the cake will create voidage, which in turn increase the chance for cake cracking. The use of water washing for salt removal could cause problems further upstream in the drying process, due to its relatively high boiling point and low vapour pressure.

2.3.5.5. Cake re-dissolution for downstream transfer

Re-dissolving the filter cake after cake washing could increase the efficiency of downstream processes. The advantage of this technique is that the solid cake no longer has to be manually transferred to the next stage in the manufacturing line. This method would require additional solvent and impurity spiking experiments to ensure downstream process robustness. The downstream unit operations should also be capable of handling a variation in solvent input and possibly a variation in impurity concentration.

2.3.6. Washing curve

Characterisation and comparison of the washing performance requires generating a wash curve by plotting the solute concentration in the liquor against a ‘wash ratio’ term. These terms are defined in equations (2.7) and (2.8) [15]:

$$\frac{C}{C_0} = \frac{Solute\ concentration\ in\ washings\ from\ the\ filter\ cake}{solute\ concentration\ in\ the\ cake\ liquor\ before\ washing\ starts} \tag{2.7}$$

$$Wash\ ratio = \frac{Volume\ of\ wash\ liquid\ used}{volume\ of\ liquor\ in\ the\ cake\ at\ the\ start\ of\ washing} \tag{2.8}$$

$$Wash\ ratio = \frac{Volume\ flow\ rate\ of\ wash\ liquor\ .Washing\ time}{Volume\ of\ liquor\ in\ the\ cake\ at\ the\ start\ of\ washing}$$

Figure 8 shows a washing curve for 3 different cases. Case 1 is the ideal profile representing perfect plug flow of wash liquor through the cake. For the ideal case there is a 100% recovery of the washing liquid and thus 100% displacement of the mother liquor. The displacement of the mother liquor in the cake shows a piston like movement. The first horizontal section of the curve represents the displacement of the mother liquor through the cake voids towards the filter. A sudden drop in concentration of solute (C/C0) occurs when the mother liquor exits the cake at Wash ratio = 1 and the volume of mother liquor is displaced by an equal volume of washing liquid. In practice a perfect plug flow in a filter cake is impossible as there will be a non-uniform dispersion. This due to different path lengths, diffusion of the mother liquor and washing solvents in the cake voids. Curve 2 is showing a typical case of a washing curve found in practice and can be divided in three distinct regions. The initial stage (A) involves the direct displacement of the retained fluid by the wash liquor. The final stage (C) occurs when a variety of local mass transfer processes in the pores of the cake take place. The intermediate stage (B) takes place when pores are subject to displacement of retrained fluid and local mass transfer processes.

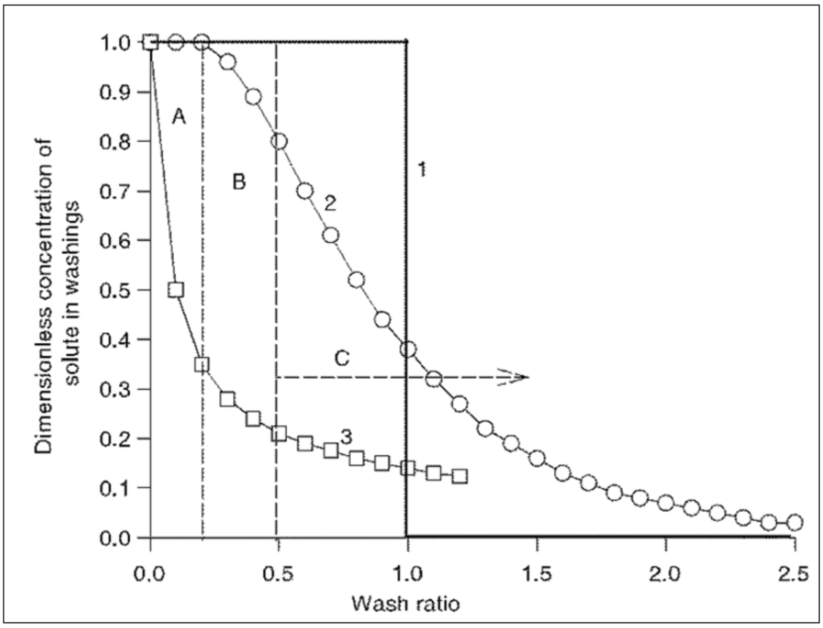

Figure 8 Wash curves (C/C₀ to Wash ratio) with 1. ideal 2. typical 3. deliquored cake [15]

Curve 3 shows a highly deliquored cake where the initial liquid has been drained. The sudden drop in concentration is explained by the low amount of absolute impurities inside the cake. With a low amount of washing liquid there will be a high concentration drop and no big displacement of mother liquor, since the pores of the cake are almost empty before washing. [15] [11] [16]

2.3.7. Wash solvent selection

Washing solvent selection is based solubility effects, physical properties and safety and environmental properties. The cake should have a low solubility inside the washing solvent. To keep the solubility of the cake in the washing solvent low, the washing solvent should be used at room temperature. This could also redress batch to batch variations. Dissolved impurities should remain in solution during the washing step and not undergo anti-solvent crystallization on the cake. High volatile washing solvents could be preferable if drying after the washing step is needed.

2.4. Centrifuge dryers

Within the project a centrifuge dryer was used to separate the cake from the mother liquor, wash and dry the cake. In centrifuge dryers the force of the centrifugal field acts as the driving force for cake formation, permeability and cake deliquoring. During filtration in the centrifugal field, this force will counteract the capillary force which retains the liquid inside the filter cake. The magnitude of this force can be controlled by changing the rotational speed of the centrifuge. Benefits of the high forces in the centrifugal field is shorter residence time of the cake [14]. Deliquoring of the residual moisture in the cake is also superior in comparison to normal filtrations. Liquid draining and applying of washing solvent are more homogenous. Disadvantages are the high forces of the centrifugal fields during the filtration. These high forces could compress the cake with the result of a lower permeability and thus increasing the washing and residence time of the cake. The compressing of the cake is heavily influenced by the morphology and size distribution of the crystals. Besides the compressing of the cake the high forces may result structural damage of fine particulate solids by removing the residual moisture inside the cake, known as the capillary rise remaining inside the porous system. [17]

2.4.1. The basic filtering centrifuge

Figure 9 shows a cutaway view of a typical filtering batch centrifuge. The main component of the centrifuge is the basket (1) with many perforations to allow the passage of the liquid during filtration. The basket also supports the filter on which the feeds solid is separated from the liquid.

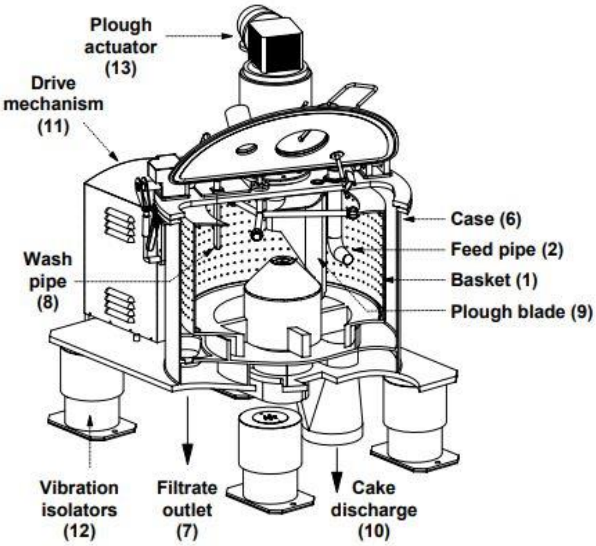

Figure 9 Schematic overview of a typical filtering batch centrifuge [18]

Figure 10 shows a schematic overview of the basket perforations (3), the filter medium (4) and the filter cake (5) in the process of being separated. The filter cake forms an annulus on the wall of the filter basket. Cake thickness is usually around 10% of the basket diameter. [19] Beside the basket many other additional components are necessary for a fully functional filter centrifuge. The additional components require to drive, support, fill, empty and enclose the basket. These components are what one filtering centrifuge type distinguishes it from another.

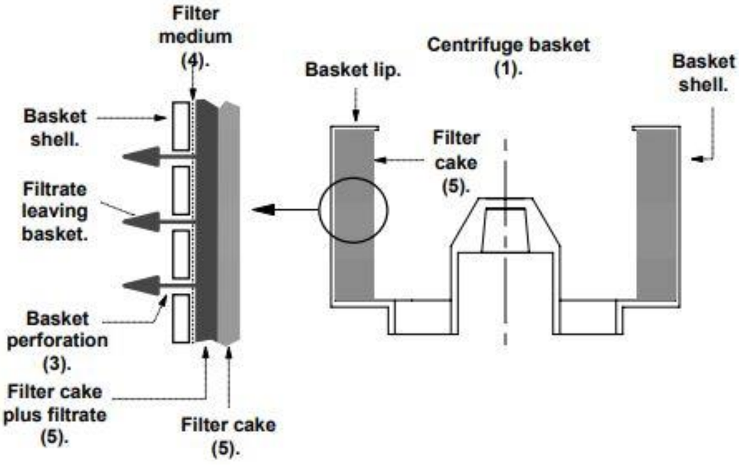

Figure 10 Schematic cross section of the basket from a batch centrifuge [18]

The basket rotates at a rate sufficient to generate an angular acceleration several hundred times the acceleration due to gravity G. This acceleration enhances the filtration process in the same way as increasing the pressure during pressure filtration would. The acceleration must result in an angular velocity higher than the minimum angular velocity for any deliquoring to occur. Typically, rotation rates for large industrial scale centrifuge with a basket diameter of 1000 mm are in the range 1000 to 1600 rpm and this generates a centrifugal acceleration equivalent to 500 to 1500G. As a comparison with a pressure filter this centrifugal acceleration is equivalent to a pressure of 10 to 30 atmospheres across a 200 mm filter cake for liquor density of 1000 kg m^{-3}. [19]

In Figure 11 a typical batch process cycle is shown. The process cycle is broken down in seven steps (2.4.1.1 - 2.4.1.7) [19] starting from an empty stationary filter centrifuge.

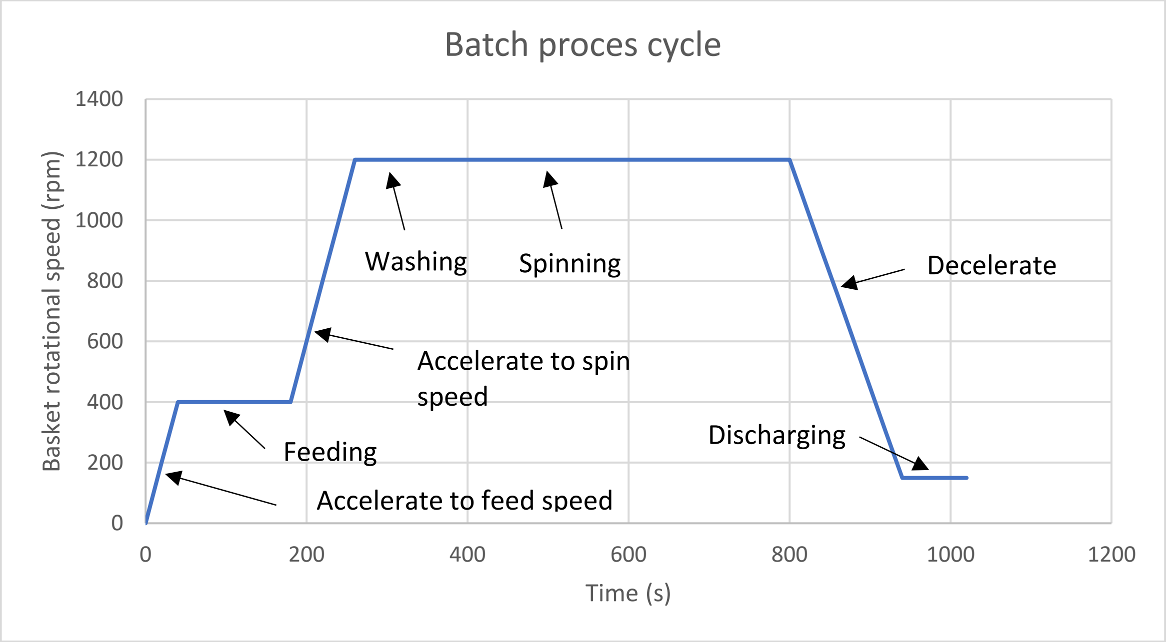

Figure 11 Example of typical batch process cycle

2.4.1.1. Feeding

Before feeding commences the basket accelerates to feed speed. Through the feed pipe (2) the slurry enters the basket and is distributed on the basket wall. The slurry forms a cake on the filter medium (4) (screen). Feeding of the slurry continues until the feed limiter detects that a pre-set weight has been reached. Slurry distribution is critical, as uneven distributed slurry could lead to ‘unbalance’ in the centrifuge. Unbalance in the centrifuge is an uneven distribution of the weight, resulting in vibrations of the centrifuge basket. Small vibrations can be silenced by the vibrations isolators, who connect the centrifuge with the surrounding structure.

The method of feeding the centrifuge basket has a big impact on both the distribution of the slurry and the level of crystal damage. Uniform distribution of the slurry and cake is of critical importance, as this will result in an even washing and drying later in the process cycle. Uneven distribution of the cake could also lead to unbalance in the centrifuge as discussed earlier.

During feeding the basket rotational speed is held constant to reduce crystal damage. Particularly needle shaped crystals are delicate for high rotational speeds. In some designs the feeding pipe turns in the same direction as the centrifuge basket to increase the even distribution of the slurry, reduce crystal damage and reduce the power consumed by the centrifuge during feeding.

Increasing the rotational speed of the basket during feeding shortens the feeding time, but has several disadvantages. High rotational speeds could result in an uneven distribution of the slurry through fast deliquoring of the cake. The slurry must remain fluid for a time to allow it to flow over the basket and give it an even distribution. In the pharmaceutical industry it is common that the feed contains a high volume of liquid and a small portion of small solid particles (20 µm). The small solid particles settle out and consolidate against the basket wall to form a cake, increasing the resistance to flow through the thickening layer of solids. If the feed speed is to high, excess liquid can form on top of the cake increasing the cycle time and chance on liquor load. [19] Liquor load is an effect that causes vibrations in centrifuge filters through spinning liquor.

To overcome problems from the excess liquid a reasonable filtration rate and centrifuge output should be maintained. Feeding can be done in burst, allowing the liquid to drain from the cake before adding more feed.

2.4.1.2. Accelerate to spin speed

The rotational speed of the basket is increased until the required spin speed for washing and spinning is reached. Deliquoring of the cake occurs as the RPM speed and thus the centrifugal forces increases. The liquid will exit the cake through the filter medium passing the perforations. It leaves the centrifuge filter through the filtrate outlet (7).

2.4.1.3. Washing

Certain processes require the cake to be washed after filtration, to achieve higher grades of purity of the cake. During the washing process it is important that the washing liquid is distributed evenly over the cake to ensure efficient washing. The washing liquid is usually applied via a series of jets on a wash pipe. The feeding pipe can be used as washing pipe, only if it’s capable of distributing the washing solvent evenly.

2.4.1.4. Spinning

After the washing step the centrifuge basket remains spinning at the same rotational speed, until the required cake dryness is achieved. The final dryness of the cake is determined by the centrifugal forces at the spin speed and the time spend drying. Beside the centrifugal force and drying time, the physical properties of the cake also influence the final dryness. Cake thickness, compressibility and particle size are the most important of these factors. The limited dryness or irreducible saturation is again defined by the physical parameters of the cake and the used washing solvent.

2.4.1.5. Deceleration

The basket is decelerated to a lower rotational speed when the required dryness has been achieved. The deceleration of the basket is done by the driving mechanism (11).

2.4.1.6. Drying

If the process requires additional drying this can be done by using a hot nitrogen flow. The feed pipe is used to introduce a hot nitrogen flow over and through the cake. Very low dryness can be achieved using this method. The disadvantage is that the seals used in the centrifuge must be capable of supporting the pressure created by the hot nitrogen flow.

2.4.1.7. Discharge

Once the basket speed has been reduced to a speed below one G a discharge or plough mechanism (9) is used to scrape out the dried product which then falls through the opening in the basket bottom and exits the centrifuge through the solids discharge outlets (10). [19]

Removing the cake from the filter medium can be done by various methods, depending on the type of centrifuge. In most of these methods there is a possibility that crystal damage will occur, especially when a blade or plough is used to remove the cake. Contact between the plough or blade and the fragile filter medium should be avoided as the filter medium could be damaged. When no contact is made with the filter medium, a small layer of crystals will remain on the filter cloth. This layer is called the heel or residual bed and in some centrifuge types it can be as thick as 5-15 mm. [19]

2.4.1.8. Filtrate clarity

When feeding the slurry onto the filter medium, the filtrate will exit through the pores of the openings in the filter medium together with crystals smaller than the openings. As feeding continues the small crystals will become trapped and form a cake, that will act as newly formed filter. The filtrate liquid passing through the filter medium will now be virtually free from suspended solids.

2.4.2. Horizontal inverting bag centrifuge

The horizontal inverting bag centrifuge is the type of centrifuge that will be used during this project. The main difference with the basic batch centrifuge is that the centrifuge basket is horizontally and the discharge mechanism is different. No plough or blade is used during ejecting the cake, minimising the crystal damage. Discharging occurs as shown in Figure 12 at low rotational speeds. The inversion of the filter medium ejects the crystal cake, leaving no residual crystals behind. This is the most important benefit of this type of centrifuge, as no residual crystal will contaminate the next batch and no cleaning of the filter medium in between batches is necessary. The inversion of the filter medium however could induce stress on the cloth, introducing rips and tears. Feeding washing and drying of the cake are similar to the basic batch centrifuge. The horizontal inverting centrifuge allows filtration of fine particles, down to less than 5 µm, but lengthens the cycle time. Relative to their basket capacity, horizontal inverting bag centrifuges require significantly more floor area than a vertical batch centrifuge.

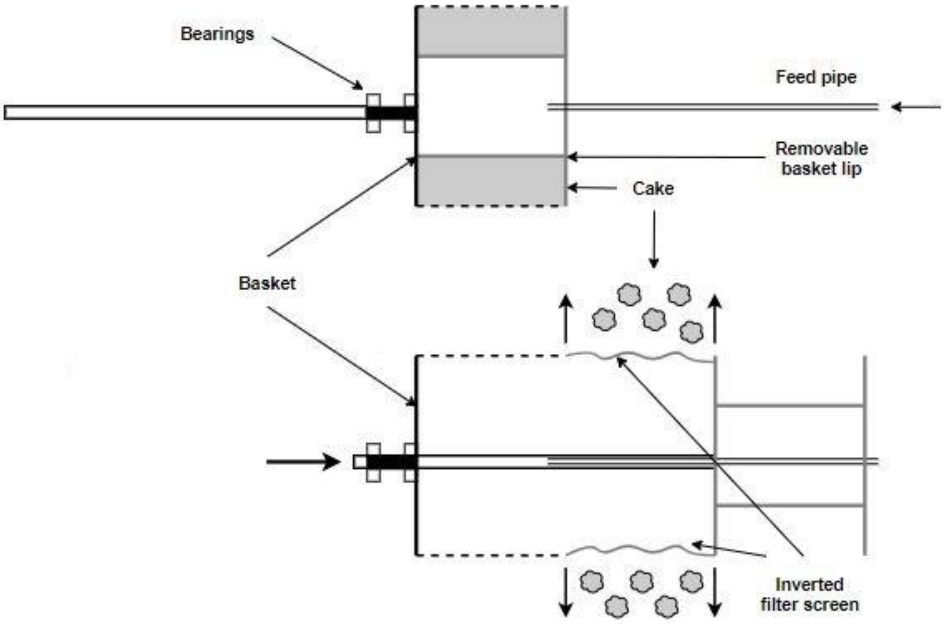

Figure 12 Schematic of inverting bag mechanism

2.5. Refractive index

Refractive index (n) is a measurement of the speed of light in a medium and how much this speed reduces in that medium. The refractive index value (n) of a medium is defines as the ratio of speed of light in a vacuum to the speed of light in that medium, as shown in equation (2.9).

$$n = \frac{c}{v} \tag{2.9}$$

A couple of examples of refractive index of solvents are shown in Table 1.

Table 1 Refractive indexes values of used solvents in this study at 20°C [20]

Solvent	Refractive index at temperature
	20°C
Methanol	1.329
Ethanol	1.362
Water	1.333
Acetone	1.359
Acetonitrile	1.344
MEK	1.379
IPA	1.377

Table 1 shows that refractive indexes higher than 1, indicating that the speed of light is lower in a medium than in vacuum. The speed of light depends on medium, temperature and wavelength. Change in medium is what is desired to measure. The common practice is to use the wavelength of 589 nm when measuring refractive indexes.

The refractive index determines how much the path of light is bent or refracted when entering a material as stated in Snell's law. In Snell's law the angle of incidence (θ_1) is the angle which the incident ray makes with the normal to the reflector or to the surface of separation. The angle of refraction (θ_2) is the angle which the refracted ray makes with the normal to the surface of separation. Snell's law states that in case of light passing from one optical medium (n_1) to another (n_2), the ratio of the sine of the angle incidence and the sine of the angle of refraction is a constant as shown in (2.10). This constant depends only on the nature of the two optical media and on the colour of the light passing through it. [21]

$$\sin(\theta_1).n_1 = \sin(\theta_2).n_2 \tag{2.10}$$

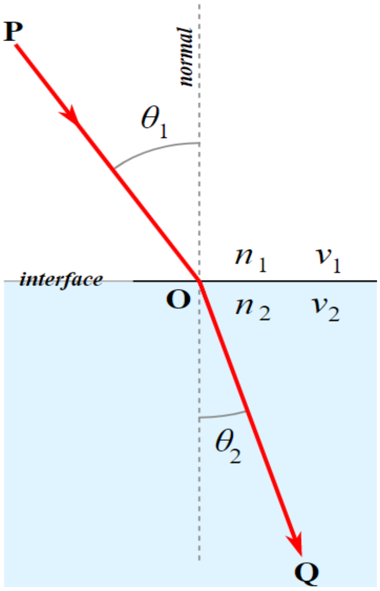

Figure 13 Schematic drawing of refraction of light from medium 1 to medium 2 [22]

Refraction of light at the interface between two media with different refractive indexes, with ($n_2 > n_1$). The velocity of the light is lower in the second medium ($v_2 < v_1$), as the refractive index value of medium 2 is higher, causing the angle of refraction θ_2 to be lower than the angle of incidence θ_1.

2.5.1. Refractometer

The measurement of the refractometer is based on the critical angle of refraction. The critical angle of refraction is the angle where all the light is reflected internally when going form a dense medium A to a less dense medium B (Figure 14). When the angle α increases, β reaches 90° and the ray travels along with the surface (Figure 14). If the angle is further increased the light cannot enter the medium B and it completely reflects into medium A. This phenomenon is called 'total internal reflection'. The angle at which $\sin\beta = 1$ is called the critical angle of refraction. [23] With the critical angle measured the refractive index of medium B can be calculated with equation (2.11) derived from Snell's law (2.10).

$$n_B = n_A \sin\alpha_c \tag{2.11}$$

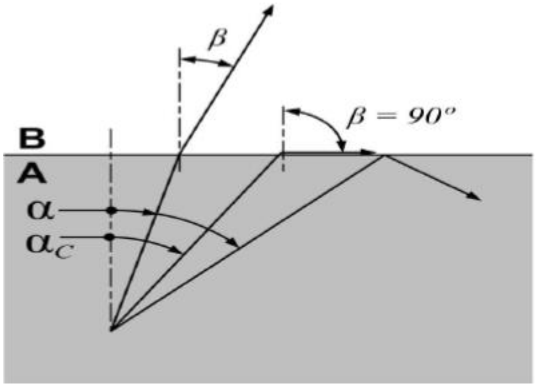

Figure 14 Schematic drawing of refractive index critical angle

To measure this critical angle α_c with the refractometer the condition of a high dense medium to a less dense medium must be fulfilled. Using a measuring prism an interface between the instrument and the medium which is measured is provided. The refractive index of the prism must be higher than this of the solvent measured, otherwise no total internal reflection will be created. If the refractive index of the prism is lower than this of the solvent the angle β will decrease relative to the normal on the interface. The used prism is exposed to the chemical environment hence it needing to be chemically and mechanically resistant.

The function of the refractometer discussed below is based on the used refractometer in this research (PR-23 of K-Patents instruments) [24]. Figure 15 show the schematic function of the refractometer, measuring the refractive index of a process medium (S). A yellow LED, providing a monochromatic wavelength of 580 nm, will be used as a light source (L). The light from the light source is directed through the measuring prism (P), to the process medium (S). The walls of the measuring prism (M) act as mirrors, causing the light rays to bend towards the medium in different angles. The light is reflected back into the process medium, as the density of the process medium is lower than this of the measuring prism.

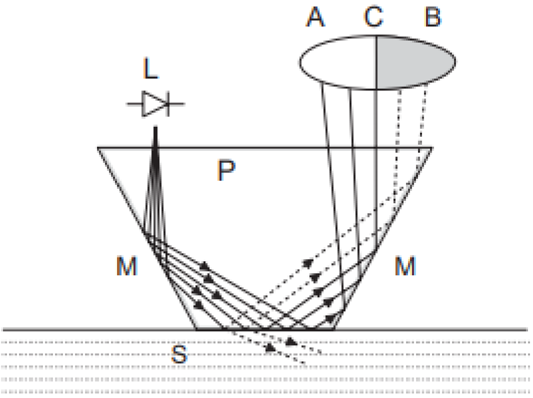

Figure 15 Schematic function of refractometer [24]

The reflected light ray from the process medium is bend on the second mirror wall (M) towards the detector. These reflected rays form an image (ACB), where C is the position of the critical angle ray. In A the rays are totally internally reflected and in B the rays are partially reflected and partially refracted into the process medium. The position of the shadow edge in C indicated the critical angle value. From this position the refractive index of the process medium can be determined by equation (2.11) as discussed above.

The refractive index value depends on the medium, temperature and concentration. Normally the refractive index will increase when the concentration increases. This also affects the critical angle and thus the optical image, as shown in Figure 16. The colour of the solution, gas bubbles, or undissolved particles do not affect the shadow edge (C).

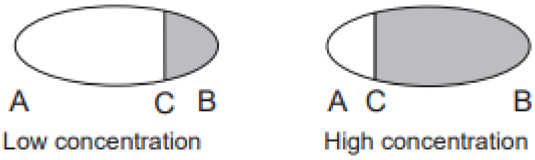

Figure 16 Relation of the concentration in solute to the optical image [24]

The measurement of the shadow edge is done digitally using a CCD element. The conversion from optical image to CCD output is shown in Figure 17. The output from the CCD is then converted to a refractive index value by a processor. The value of the refractive index of the process medium, together with the temperature of this medium, is transmitted to the display and system.

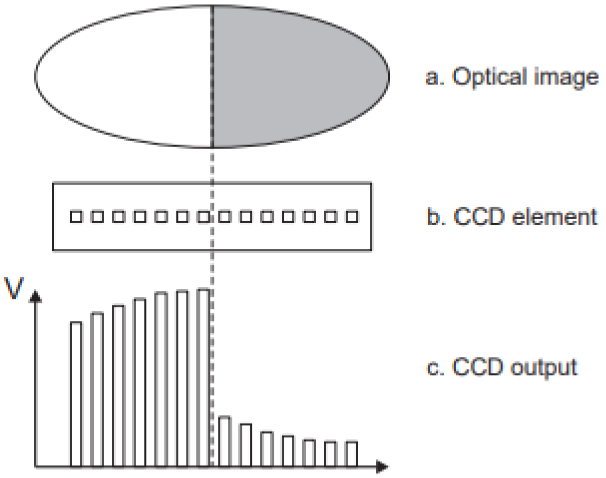

Figure 17 Measurement of shadow edge using a CCD element [24]

2.6. **Process Analytical Tools**

Process Analytical Technology/Tools (PAT) is a system for analysis and control of manufacturing processes based on timely measurements of critical quality parameters, performance attributes of raw materials, and in-process products to assure acceptable end-product quality at the completion of the process as defined by the Food and Drug Administration (FDA). [25]

The goal of the implementation of PAT is to increase the product quality, increase the process knowledge and decrease the frequency of batch to batch variations. [8] A process is generally considered well understood when (1) all critical sources of variability are identified and explained; (2) variability is managed by the process, and (3) product quality attributes can be accurately and reliably predicted over the design space established for materials used, process parameters, and manufacturing, environmental, and other conditions. [25]

Real time measurements with PAT can be done in three different ways [25]:

1. at-line: a sample is removed from the process stream and is analysed in close proximity of this process stream;
2. on-line: the sample is diverted from the process stream by a loop, analysed in this loop and later returned from the loop to the process stream;
3. in-line: measurement by the PAT is done without removing the sample from the process stream. This measurement by the PAT can be done invasive by introducing a probe and disturbing the process stream, or noninvasive, where the sensor does not come into contact with the material and the process stream is not disturbed.

PAT implementation can be used during different stages in pharmaceutical manufacturing. Table 2 describes the differences between the use of PAT in development and manufacturing. During the early stages of development, the analyses of the process is complex as critical parameters are not yet defined. As the process is more defined during later stages of the research, the number of suspected critical parameters can be reduced. As the development reaches the first stages of manufacturing, PAT can already be implied. During this stage in development, the process parameters control limits are established. Ideally the PAT is directly correlated with manufacturing parameters, such as time, pressure, temperature, to control the process. If no direct or ideal correlation can be found between PAT and the process parameters, PAT may still be installed to acquire information for process scale-up, optimization, transfer, fault detection and fingerprinting for later use. The early use of PAT in the manufacturing process as fingerprinting, may greatly benefit the process for advanced trending and control or to understand unexpected deviations. [26]

Table 2 PAT use in development and manufacturing [26]

	Development	**Manufacturing**
Overal purpose	Understand	Control, trend analysis
Desired technology	Multicomponent analysers	Target analysers
Data complexity	Multivariate	Univariate, or multivariate
Support requirements	High level expertise continuous support	Robust and automated minimal support
PAT expertise	Method design and development	Operation and maintenance

2.6.1. Advantages in PAT Implementation over Traditional Methods

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 improve the 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, by introducing real time measurements without any destruction of the sample.

However, implementation of PAT at the industrial scale requires time and cost-intensive modifications to the design in the manufacturing process. [8] Additionally, a deep understanding of the process is needed to analyse this newly acquired data. The data provided by the PAT should be studied and analysed to understand how process parameters and deviations affect the measurements of the used PAT. [18] This may require implementing PAT in the early stages of the R&D to ensure sufficient data later in the development process as discussed earlier (2.5). [19]

Traditional sampling methods for analysing the process stream uses large amounts of materials, intermediates and finished products resulting in time consumption, batch delays and yield loss. In most chemical plants, analysing samples from the process stream is done in a laboratory and not instantly besides the process stream. The analysing by the separate laboratory causes significant time consumption. PAT allows instant analysing of the process stream without the need for large sample size or destruction of the taken sample. Detection of deviations and adjustment of the parameters can be done instantaneously, as no time is needed for sampling and sample prep in the laboratory. [27] Beside the instant measuring and non-destructive sampling, PAT provides another significant advantage. PAT can provide measurements of parameters that are difficult or undesirable to measure, e.g. highly toxic and hazardous materials, high pressure systems, low or high temperature systems, … with standard off-line techniques. [26]

PAT coupled with risk-based strategies prevents the chance on poor product quality. Critical parameters are identified and measured with the implementation of the PAT and can be adjusted to achieve the value in order to ensure the quality of the product. The process is then validated according to the process parameters under controlled environment. Any deviations to the set process parameters will be measured and can be adjusted instantly to prevent unacceptable product quality. The coupling of PAT with the set process values allows for a controlled process stream and instant detection of any deviations. [27]

2.6.2. PAT in filter cake washing

As discussed earlier PAT can be used for on-line monitoring of differenct manufacturing processes in the pharmaceutical industry. As cake washing is a manufacturing process that is hard to predict, PAT implementation could be useful to detect any deviation and provide process control. In 2.6.2.1 and 2.6.2.2 different PAT's, that can be used for this on-line monitoring, will be discussed.

2.6.2.1. Raman spectroscopy

A widely used PAT for real-time monitoring of critical process parameters in pharmaceutical processing is the Raman spectroscopy. Because of the non-destructive nature and instant measurement of the Raman spectroscopy, on-line monitoring poses no problem. Using a Raman probe, equipped with chemical resistant materials and fibreoptic cables, in-line measuring of the process is possible. There is a wide range of processes in which Raman spectroscopy as a PAT can be implied, such as blending, granulation, drying, washing, coating, etc. [28]

Raman spectroscopy is a technique used to observe vibrational, rotational and other low-frequency modes of a system. The technique relies on Raman scattering of monochromatic light. The monochromatic light interacts with the vibrations or rotations of the sample and shifts up or down in energy level. This change in energy level is measured and gives information of the vibrational and rotational modes of the system.

Raman spectroscopy in-line monitoring of cake washing, provides a method to determine washing curves, which could be further used to optimize filter cake washing, as discussed in 2.3.6. Another capability of the Raman analyser is the measurement of cake dryness, which can be linked to the degree of deliquoring of a cake. If indeed strong deliquoring has occurred before the washing, then this could influence the washing process, as discussed in Figure 8 in 2.3.6. [16]

2.6.2.2. Refractive index

Refractive index measurements to determine the concentration in a solute are used in HPLC. However, refractive index is only used in specific set ups. The use of refractive index as a PAT in cake washing is relatively new. Refractive index has been used to monitor the API concentration in solvent to determine the MetaStable Zone Width (MSZW) of a batch cooling crystallization process. [8] As discussed earlier, in most cases of PAT implementation in cake washing, Raman spectroscopy is used

2.6.3. PAT for end point determination

Within the PAT framework, a process endpoint need not be fixed in time, but can be the achievement of a set process value of the critical parameter or material attribute. This however, does not imply that time should not be considered. During development of the process and manufacturing, knowledge and data over process time windows is likely to be acquired. [25] PAT as a method for end point determination can be used for different manufacturing process, such as tablet coating and drying. [29] [30]

The goal of end point determination using PAT is an automated process, in which human interaction is only needed when large deviations are detected. This is possible in 2 ways: end point based on a process parameter or the use of a theoretical model. Using the first way, the end point is reached when the set process value of a critical parameter or material attribute is achieved. This end the process and the software will proceed to the next step or signal that the process has ended. This is an easy use of the PAT, as only the set process value must be reached. The problem however is that there is no feedback control of the process. For example, the set process value can be reached due to deviations without reaching the real end point of the process. Using the second way for end point determination, requires a lot of process knowledge and data. The software can follow the theoretical curve, not only determining the end point, but also any deviations.

3. Materials and Methods

3.1. Products and Solvents

The products that will be studied are Alios T3728, Alios T3730 and Alios Crude. The characteristics of these products will be discussed in 3.1.1.

Products are divided into 4 isolation classes, class A for easy filterable products with low resistance, until class D for products that are very hard to filter with high resistance and compressibility. Table 3 shows the different classifications for filter products and remarks that have to be taken into consideration when filtering this type of product.

Table 3 Isolation classification

Classification product	Comments on filtration
A	Fast filtration Maximum cake height can be used during filtration and centrifugation Maximum centrifuge rpm speed can be used Due to larger particle size and tendency of the slurry to settle, care should be taken to imbalance in the centrifuge and settling of the particles during transport
B	Lower rpm speed of centrifuge Maximum cake height
C	Lower rpm speed of centrifuge Reduce cake height
D	Low centrifuge rpm speed due to high cake compressibility Attention should be paid to filling weight, due to high cake resistance Crystallization should be redesigned to increase particle size and morphology

3.1.1. Alios 8176

The products Alios T3728, Alios T3730 and Alios Crude will be discussed in detail below.

3.1.1.1. Alios T3728

The properties of the ‘Alios 8176 T3728’ product are summarised in Table 4.

Table 4 Product properties and parameters of Alios 8176 T3728

Product property/parameter	**Alios T3728**
Crystal morphology	Hair-like (Figure 18)
Crystallization process	Robust process
Washing solvent	IPAc/Heptane 1:4 vol
Isolation classification	D (high resistance, compressible)
Amount of washing solvent (l/kg)	1.98
Solubility of product in washing solvent (g/l)	0.8

The crystal structure of Alios T3728 is hairlike, as shown in Figure 18.

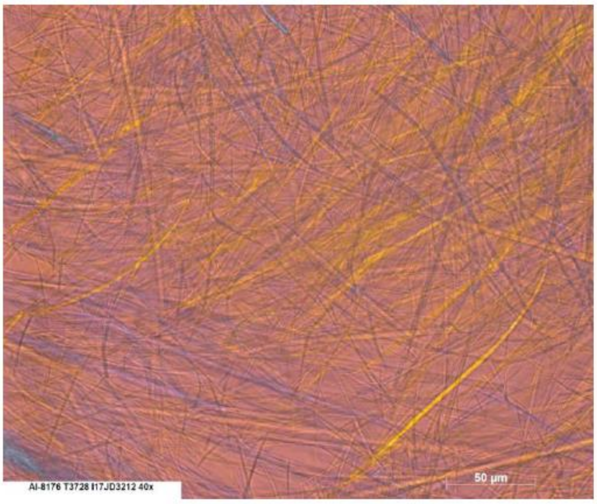

Figure 18 Microscopic picture of Alios 8176 T3728 crystal structure

3.1.1.2. <u>Alios T3730</u>

The properties of the ‘Alios 8176 T3730’ product are summarised in Table 5.

Table 5 Product properties and parameters of Alios 8176 T3730

Product property/parameter	**Alios T3730**
Crystal morphology	Rod-like (Figure 19)
Crystallization process	Time dependent (filtration within 24h)
Washing solvent 1	Acetonitrile/Water (1:2.5 vol)
Washing solvent 2	Water

Isolation classification	A (low resistance, not compressible)
Amount of washing solvent 1 (l/kg)	1.8
Amount of washing solvent 2 (l/kg)	1.9
Solubility of product in washing solvent (g/l)	2.3

The crystal morphology of Alios T3730 is rodlike as shown in Figure 19.

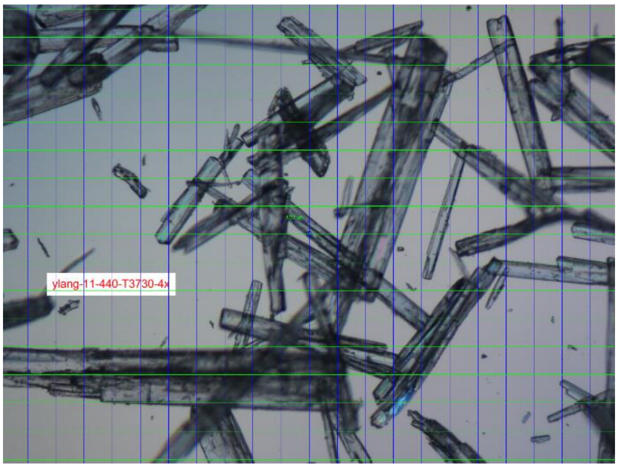

Figure 19 Microscopic picture of Alios 8176 T3730 crystal structure

3.1.1.3. Alios Crude

The properties of the ‘Alios 8176 Crude’ product are summarised in Table 6.

Table 6 Product properties and parameters of Alios 8176 Crude

Product property/parameter	Alios Crude
Crystal morphology	Rod-like (Figure 20)
Crystallization process	Robust
Washing solvent 1	Acetonitrile/Water (1:4 vol)
Washing solvent 2	Water
Isolation classification	A (low resistance, not compressible)
Amount of washing solvent 1 (l/kg)	5.013
Amount of washing solvent 2 (l/kg)	2.26
Solubility of product in washing solvent (g/l)	1.9

Alios Crude has a similar crystal structure as Alios T3730 as shown in Figure 20.

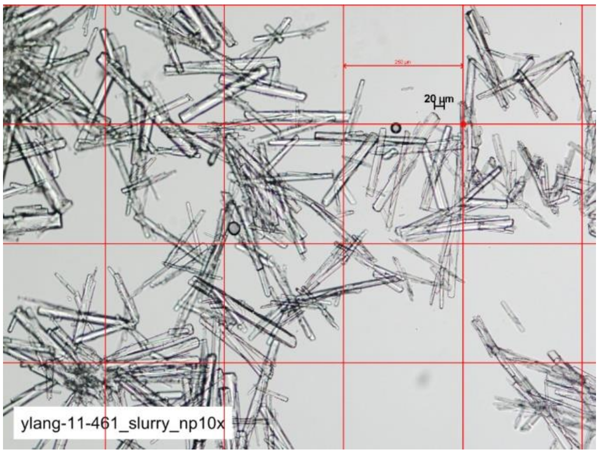

Figure 20 Microscopic picture of Alios 8176 Crude crystal structure

3.1.2. $NaHCO_3$

$NaHCO_3$ was used as a product to test the influence of different process parameters during pilot tests. $NaHCO_3$ was chosen because it is a cheap product with a large particle size. In addition, a lot of the characteristics, such as solubility in solvent, of $NaHCO_3$ are known. $NaHCO_3$ is a low resistance product and causes no problems during filtration as compressibility of the filter cake is limited. The product is a class A filtration product.

The used washing solvents to wash the $NaHCO_3$ filter cake are listed in Table 7. Besides the used washing solvents, the solubility of $NaHCO_3$ in each washing solvent is also given. Other properties of $NaHCO_3$ are not discussed as they do not influence the filtration and washing.

Table 7 Solubility of $NaHCO_3$ into tested washing solvents

Washing solvent	Solubility of $NaHCO_3$ (wt%)
Methanol	2.13
Ethanol	0.00
Water	8.76
Acetone	0.02

3.1.3. Solvents

Table 8 shows the refractive indexes of the pure solvents at 20°C. [20]

Table 8 Refractive indexes of the pure used solvents at 20°C

Solvent	**Refractive index at 20°C**
Methanol	1.329
Ethanol	1.362
Water	1.333
Acetone	1.359
Acetonitrile	1.344
MEK	1.379
IPA	1.377
Heptane	1.387
IPAC	1.377

3.2. Materials

3.2.1. Centrifuge dryer Heinkel

In this paragraph the function of the centrifuge dryer will be discussed in detail. In this study horizontal inverting centrifuge dryers by HEINKEL drying & separation group were used. A distinction is made between the centrifuge dryer used in module A and the centrifuge dryer used in module B. Module 1 and module B are the different parts in the CDPP plant. Each module has different technical parameters. The set up in the CDPP plant is shown in Figure 21, where the reactors and centrifuge dryers are colour coded by module and material.

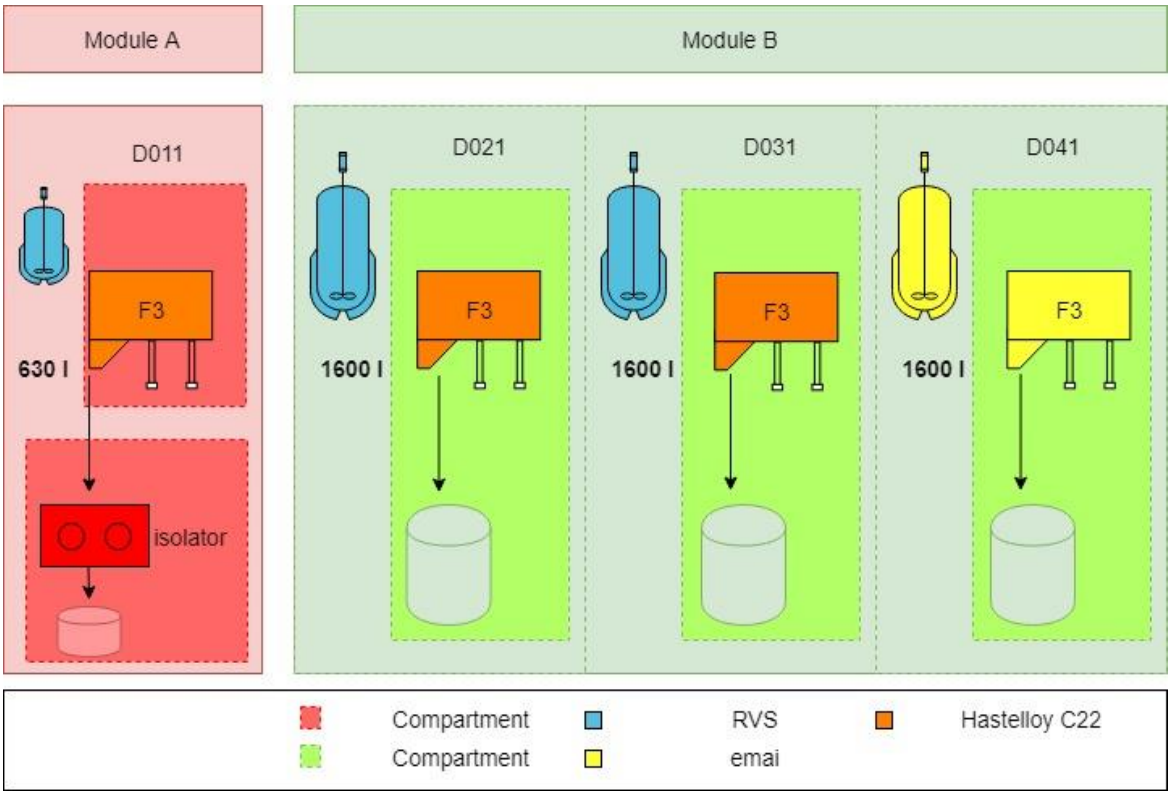

Figure 21 setup centrifuge dryers in CDPP for module A and B

The difference between module A and B is the products that are processed in each module. Final products and dangerous substances, such as fentanyl, are processed in module A. Hence the increased safety precautions and separation from the remainder of the building. Intermediates and products that are produced in large quantities, are processed in module B.

Figure 21 shows that the centrifuge dryers consist out of different materials, such as stainless steel (RSV), Hastelloy and emai.

The centrifuge dryers are fed from the reactor with slurry. These reactors are almost always the reactors one level above the centrifuge dryers in the same compartment. Rarely a slurry is fed to the centrifuge dryer from a different compartment than its own. This is done to avoid contamination and human error. The feeding of the centrifuge dryers from the reactor vessels is discussed further below in 3.3.1.1.

In the CDPP plant Heinkel F1 (module A) and F3 (module B) types are available as shown Figure 22 Figure 23. In the CDPP plant the standard types from Heinkel were remodelled to fit the specific needs of the plant, such as adding a peephole, sampling device, …

Figure 22 picture of centrifuge dryer Heinkel type F1 in module A

Figure 23 picture of centrifuge dryer Heinkel F3 in module B

Dimensions of the type F1 a type F3 are given in Table 9.

Table 9 technical parameters centrifuge dryer Heinkel type F1 and F3

Process parameter	Heinkel type F1	Heinkel type F3
Diameter basket (mm)	450	710
Depth basket (mm)	220	350
Revolutions/min (rpm)	350-2700	225-2000
Max G-force (N)	1837	1590
N2 flow (Nm³/h)	70-400	120-1000
N2 max pressure (barg)	4	6

Inlet temperature (°C)	20-80	20-80
Max batch size (kg)	34	129
Filtration area (m²)	0.31	0.78
Material	Hastelloy C22	2 units Hastelloy C22 1 unit SS316
Filter screen	Sefar tetex Multi 05-12-330 W Pharma polypropylene	Sefar tetex Multi 05-12-330 W Pharma polypropylene

Only type F3 will be used, because type F1 is only used with end and dangerous products. These products will not be studied in this research.

The schematic section of the centrifuge dryer is given in Figure 24. The different components are summarised in Table 10.

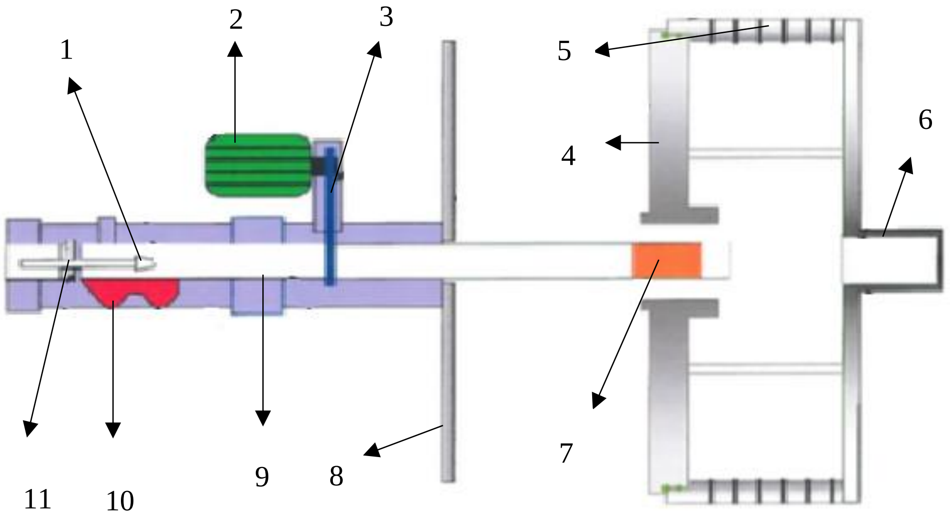

Figure 24 Section of centrifuge dryer feeding pipe and centrifuge basket [31]

Table 10 Components of section of centrifuge dryer (Figure 24)

Number on Figure 24	Component
1	Nozzle for cleaning Teflon sleeve
2	PAC Drive
3	Drive belts
4	Basket insert

5	Centrifuge bowl
6	Teflon sleeve
7	Radial membrane
8	Front wall solid housing
9	Rotating feed pipe
10	PAC chambers
11	Axial membrane

3.2.2. Refractometer PR-23

In this study an inline refractometer PR-23-62 of K-Patents Instruments will be used. Figure 25 shows a cutaway view of the refractometer PR-23. As discussed earlier in 2.5.1, the refractometer works with a prism (A) to measure the liquid. All optical components are mounted inside the core module (C), which is protected by the framework. The prism is springloaded, in the core module, against the prism gasket (B). To protect electronics against the possible heat of the process, cooling fins (G) and thermal isolators (K) are added. A yellow LED, providing a monochromatic wavelength of 580 nm, is used as a light source (L). The light is received by the CCD element (E). The Pt-1000 is used as a temperature probe (F) to measure the temperature of the process stream. Raw data from the CCD element and the temperature probe, are collected by the sensor processor card. Here the refractive index and process stream temperature are calculated and send to the server. [24]

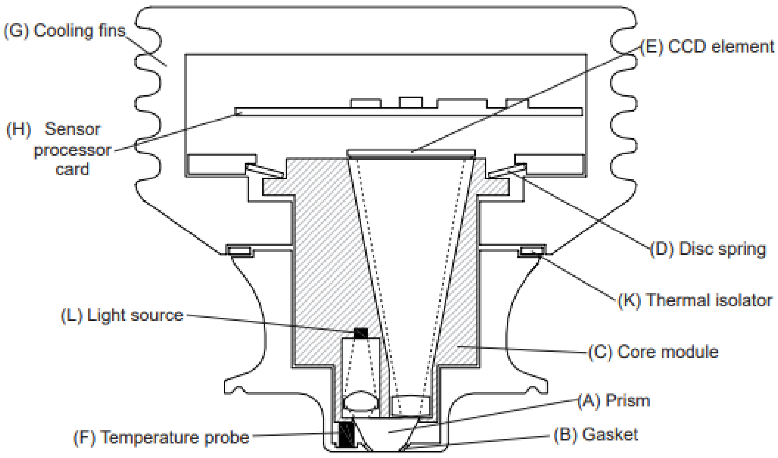

Figure 25 Sensor structure of refractometer PR-23 [24]

Table 11 shows the technical data, such as range, accuracy, of the PR-23 refractometer.

Table 11 Technical specifications of refractometer PR-23 [24]

Specifications	Refractometer PR-23
Refractive index range	1.3200 – 1.5300
Type of prism	Standard prism
Accuracy	0.0002
Speed of response	1 s undamped, damping time selectable up to 5 min
Light source	Light emitting diode (LED) 589 nm wavelength, sodium light
Temperature sensor	Built-in Pt-1000
Temperature compensation	Yes

Refractometers can be equipped with a standard prism or a sapphire prism. Standard prism refractometers have a refractive index range of 1.3200 - 1.5300. Sapphire prism refractometers have a refractive index range of 1.2600 - 1.5000.

The refractometer PR-23 is equipped with a built in Pt-1000 temperature sensor and a temperature compensation model. The temperature compensation model uses a temperature compensation to adjust the refractive index. The temperature compensation factor is calculated using (3.1).

$$\frac{-\delta y}{\delta x} = T_{coeff} \tag{3.1}$$

With y = nD refractive index and x = temperature (°C). A standard temperature compensation of -0.0001 nD in refractive index for the increase of 1°C in temperature can also be implemented. This standard temperature compensation is not liquid specific and was measured using water. Organic solvents could deviate from this compensation and show a larger or smaller temperature effect on the refractive index.

The built-in relays send an electrical signal to the server system. The refractometer uses the 3.8 to 20.5 mA output signal range for measuring information, with ≤3.6 mA or ≥21 mA indicating failure, as shown in Figure 26. With this information it is easy to detect whether the refractometer has failed or there is an empty pipe. As the refractive index of gasses cannot be measured, the refractometer will output a 3.8 mA. The corresponding RI value will indicate a 0 and not a failure.

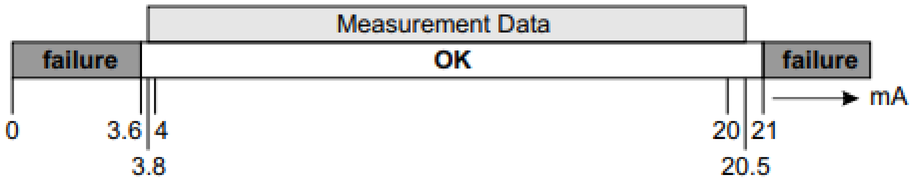

Figure 26 Default mA output values [24]

uses the 3.8 to 20.5 mA signal range for measurement information, with ≥21 mA or ≤3.6 mA to indicate diagnostic failures (see Figure 6.11). With that information, it is easier to detect a failure condition on a refractometer, for example, it clearly tells you whether you have an empty pipe or a failed instrument. [24] The output values of the refractometer between 4-20 mA are used to signal the refractive index value.

The standard setup is shown in Table 12.

Table 12 Refractometer relation of refractive index to output (mA) [24]

Refractive index value	output (mA)
Default	3.8
1.3200 (min)	4
1.5300 (max)	20

The refractometer PR-23 is mounted after the centrifuge dryer. The place of mounting in the process is shown on Figure 27 . The mother liquor or washing liquid exits the centrifuge dryer, passing through XV44 and the refractometer, to the mother liquor tank. PR-23 measures the refractive index and temperature of the passing liquid. The data is sent to the server and can be viewed in Osisoft processbook PI.

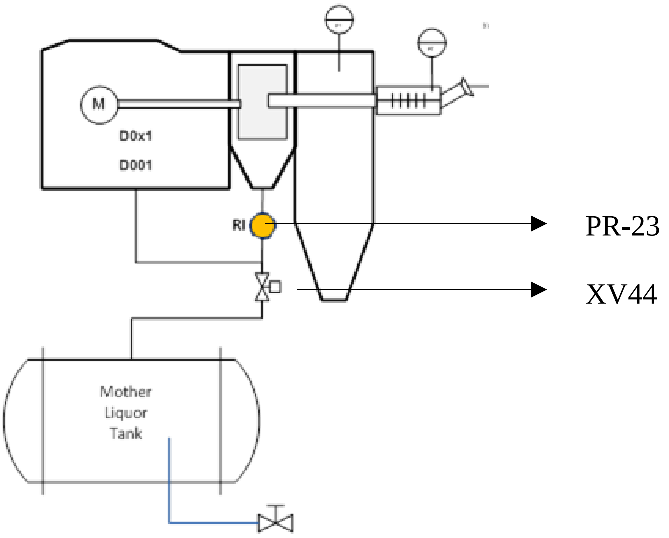

Figure 27 Process diagram of placement of PR-23 relative to centrifuge dryer [32]

3.2.3. OSIsoft processbook PI

All the collected data from the CDPP can be viewed using ‘OSIsoft Processbook PI’ (PI). The software allows the user to recall any data measured in the past. When given a tag number of specific process parameter (5) and a timeframe (1-4), PI will produce the data measured in the process. This data can be displayed using a trend, an example of such a trend is shown in Figure 28.

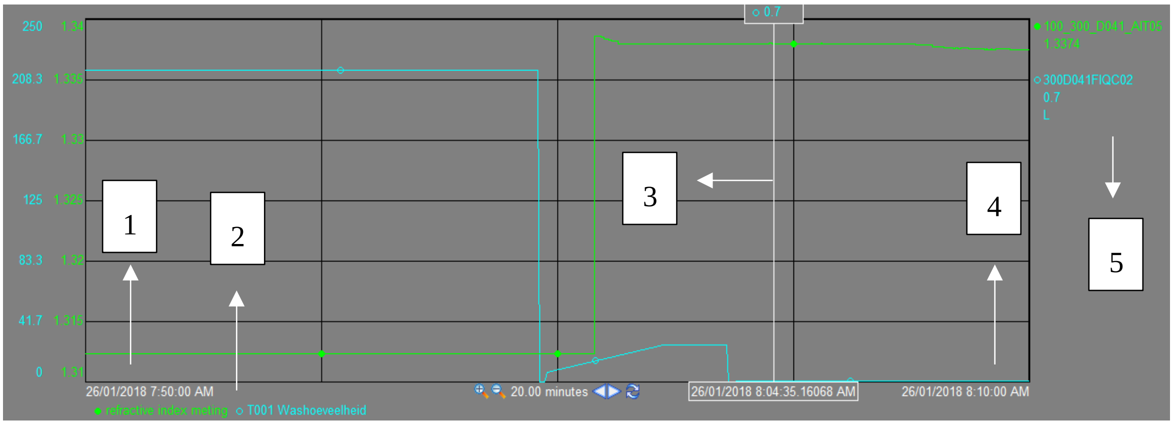

Figure 28 Example of a washing trend in OSIsoft Processbook PI

All process parameters are colour coded to distinguish them from each other (2). As shown on Figure 28, it is also possible to precisely measure the value of the parameter at a set time using the 'vertical line tool' (3). The time of that data point is also given at the bottom of the vertical line.

3.3. Methods

3.3.1. Unit operations centrifuge dryer

This paragraph will discuss in detail the filtration, washing and drying of the slurry. In particular, the method that is used during this research at Janssen Pharmaceutica for separation and cleaning of the crystals.

The unit operations of the centrifuge dryer are the following:

1. Filling of the centrifuge
2. Washing of the filter cake
    a. Technical wash
    b. Reactor wash
    c. Normal wash
3. Pressurized Advanced Centrifugation (PAC)
4. Drying
5. Discharge

Since the reactor vessel is larger than the centrifuge dryer, the batch is separated into loads. For each load, all unit operations are run through. One batch could have up to 9 loads to process. The amount of loads depends on the amount of product and the filtration classification of the product. Products with a filtration classification of C or D require more loads, as the cake resistance obstructs fast deliquoring of the cake.

3.3.1.1. Filling

The centrifuge dryer is filled using the pathway shown in Figure 29. The batch in the reactor vessel is separated into different loads. For each load the centrifuge dryer is filled with the product slurry from the reactor vessel through the pathway colored in orange. The product slurry is fed through the feed pipe into the centrifuge basket. A detailed description of the different components in a filtering centrifuge is given in 2.4.1.

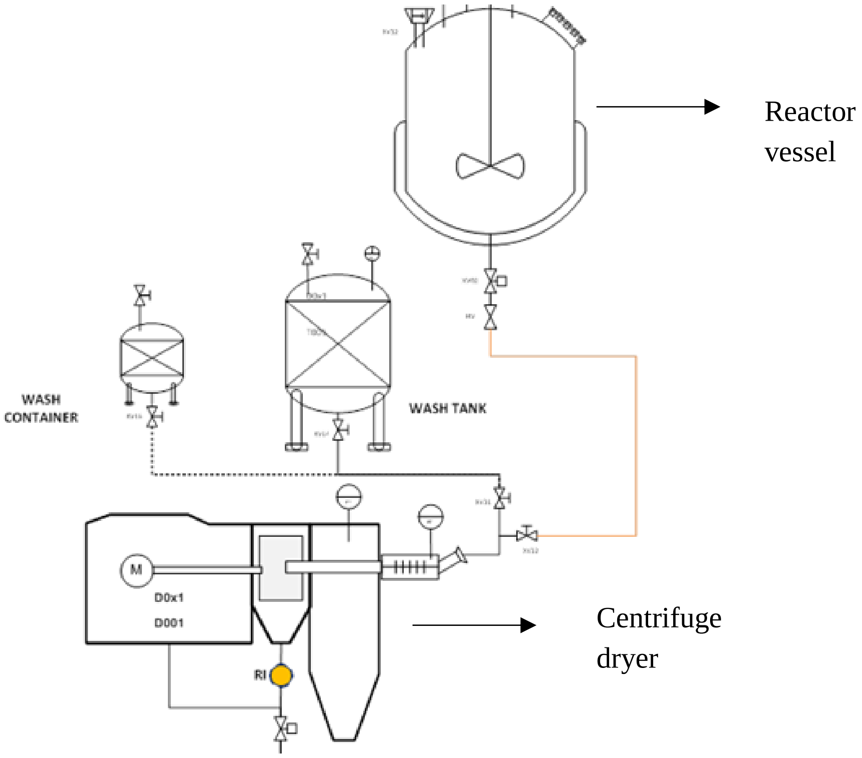

Figure 29 Process diagram filling of centrifuge dryer from reactor vessel [32]

The product slurry enters the filtering centrifuge through the feeding pipe shown in Figure 30.

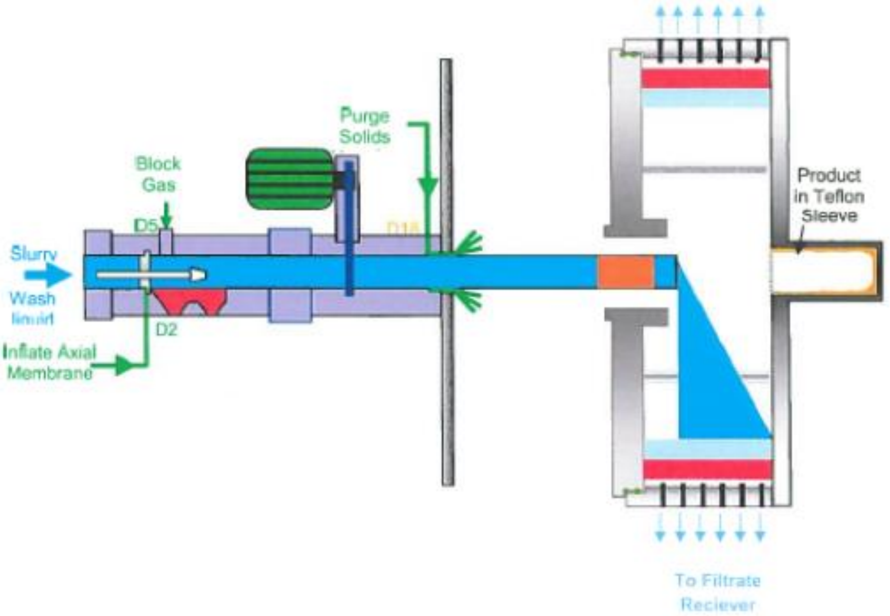

Figure 30 Section of centrifuge dryer during feeding through feeding pipe [31]

Figure 32 provides a schematic overview of the filling of the centrifuge. Before filling the centrifuge dryer an estimation of the number of loads needed for total filtration of the slurry in the reactor is made. This estimation is based on the isolation classification of that product that needs to be filtrated.

The selected load size is an estimation as optimization of the filling weight is done during processing of the slurry. The filling of the centrifuge dryer is weight based. An example of the centrifuge dryer weight during filling is shown in Figure 31. A minimum and maximum weight is set as a process parameter. The centrifuge dryer is filled until the maximum weight is reached. After the filling of the centrifuge dryer with the slurry, the excess liquid will drain from the filter cake, as the centrifuge is spinning at a set speed. The excess liquid will be collected in the mother liquor tank. This causes the weight to drop. If the weight in the centrifuge dryer drops below the minimum set weight limit, the centrifuge dryer will start to refill again. This cycle is repeated until the minimum weight is not reached within a set time limit. Each filling of the centrifuge dryer, the speed of deliquoring of the cake decreases. The decreasing deliquoring cake is caused by the increased number of solids, thus increasing the resistance of the filter cake. This increases resistance of the filter cake causes the deliquoring to slow down. As discussed in 3.3.1, the filtration classification of the products influences the filling process heavily. Products with the filtration classification C or D have a high cake resistance. This increased cake resistance will lower the deliquoring speed of the excess liquid, causing the minimum weight not the be reached in the set up time frame. The product batch will have smaller load size and thus an increase in the number of loads.

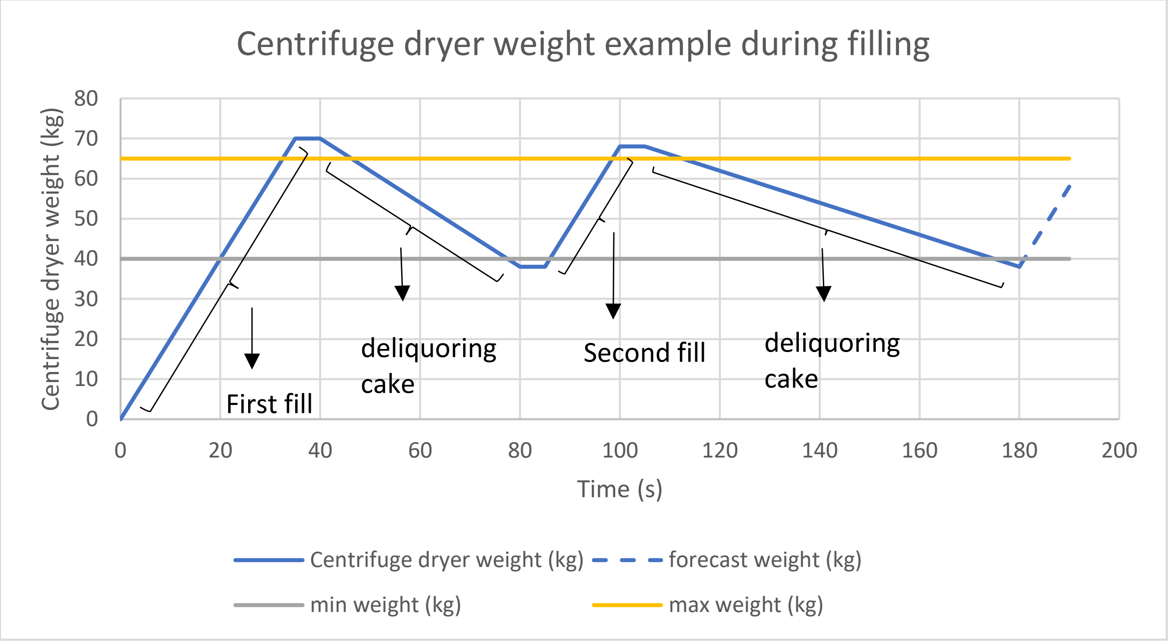

Figure 31 Centrifuge dryer weight during filling example trend

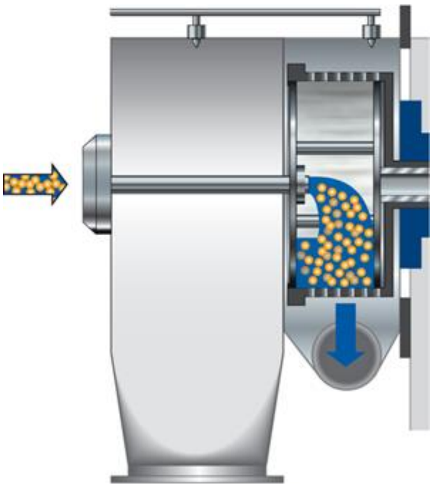

Figure 32 Filling of the centrifuge dryer, schematic overview [17]

After fully filling the centrifuge dryer, the filter cake is spun at an increased speed to remove any excess liquid before the washing step commences. The removal of this excess liquid, decreases the amount of washing liquid that will be needed for cleaning the filter cake. Mixing between washing solvent and mother liquor will also be significantly less if excess mother liquor is removed before washing.

After the filling of the last load of the batch into the centrifuge dryer, a reactor can be done. The reactor wash is done to remove any residual product in the reactor, to decrease product loss. The reactor wash is done with 40 L of washing solvent after the filling and before the washing.

3.3.1.2. **Washing**

The filter cake is washed with a washing solvent, to remove any impurities entrapped in the cake. A schematic overview of the process is shown in Figure 33.

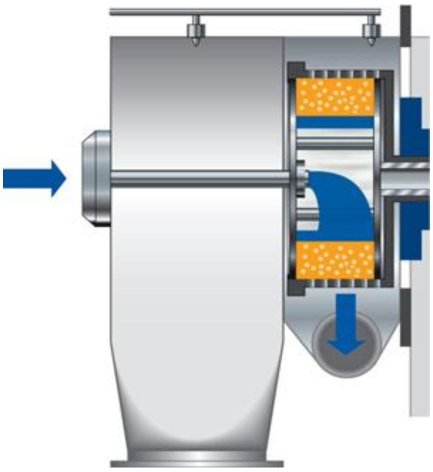

Figure 33 Washing of filter cake, schematic overview [17]

A cake washing in the centrifuge dryer is done in several steps.

Reactor wash

Washing solvent is used to collect residual product in the reactor vessel, this process is called a reactor wash. A set amount of washing solvent, which is the same as the washing solvent used during the normal washing step, is used for cleaning any residue. The reactor washing solvent is done before the technical and normal washing as is shown in Figure 34. The orange curve shows the amount of washing solvent that is used when a reactor wash is done. The sharp increase in washing solvent at 65 s is the 40 L of washing solvent that is added for reactor washing. The blue curve shows the washing amount when no reactor washing is done. The amount of washing solvents that is added resets each time a new washing is done. For the blue curve, the first washing is the technical wash. No washing solvent is added before the drop to 0 at 2850s.

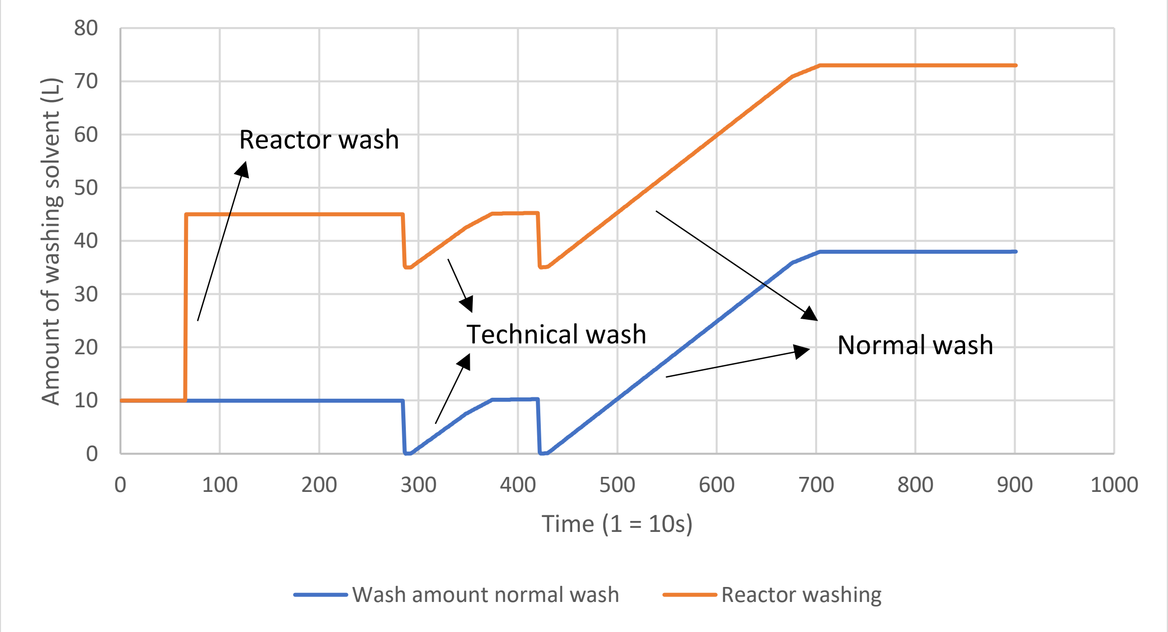

Figure 34 Washing trend example - Reactor washing

The reactor washing uses the feed pipe as a pathway to the centrifuge dryer. The washing solvent and residual product are fed into the centrifuge dryer over the spinning filter cake. Reactor washing is done between filling of the centrifuge dryer and washing of the filter cake.

Reactor washing is only done in the last load to the centrifuge dryer of a certain batch. Additionally, there must be a large amount of residual product for reactor washing to be carried out, as this requires additional washing solvent.

Technical wash

Figure 35 shows a washing trend within the centrifuge dryer. The amount of washing solvent that is added is shown on the y-axis. The time is shown on the x-axis. The amount of washing solvents that is added resets each time a new washing is done. The technical wash is the first wash. No washing solvent is added to the filter cake before the amount of washing solvent drops to 0 at 110s.

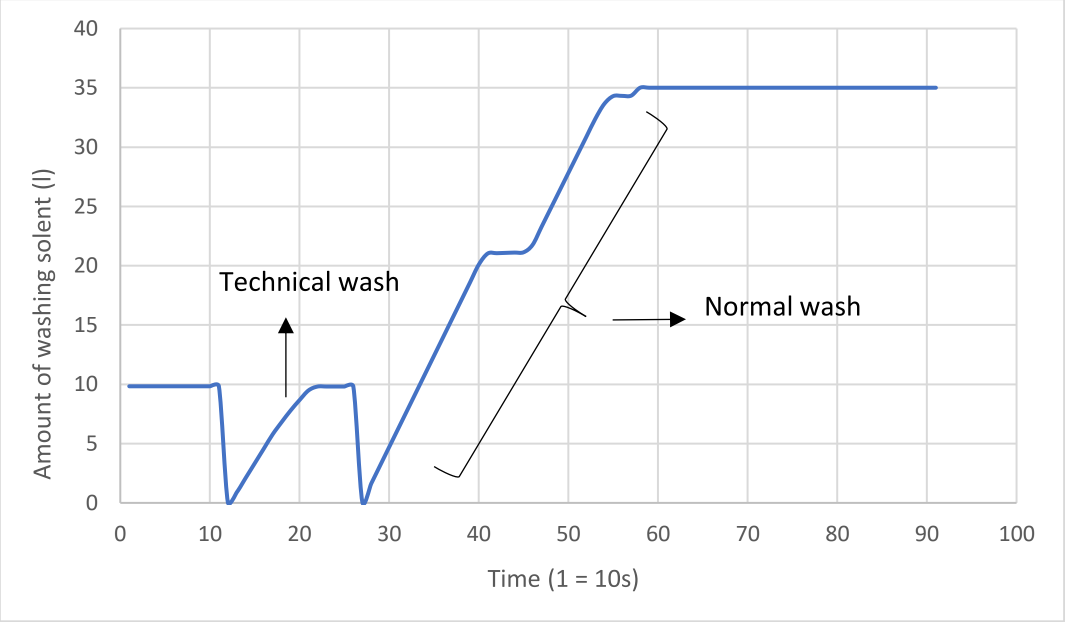

Figure 35 Washing trend example with technical wash and normal wash

First, a technical washing is done. The washing amount resets to 0 at the start. In every case of a technical wash a volume of 10 L of washing solvent is used. The washing solvent used for technical washing will be the same as the first washing solvent used in the normal wash step, if multiple washing solvents are used. The purpose of this technical wash is done to remove any crystals that have formed at the end of the shaft. Cleaning the shaft allows for smooth inverting of the filter cloth during ejection of the filter cake. The inverting filter mechanism is discussed in detail in 2.4.2 and Figure 12. Technical washing is done through the washing lance shown in Figure 36. The technical washing lance is located inside the feeding pipe. Residual product from the shaft is washed onto the filter cake.

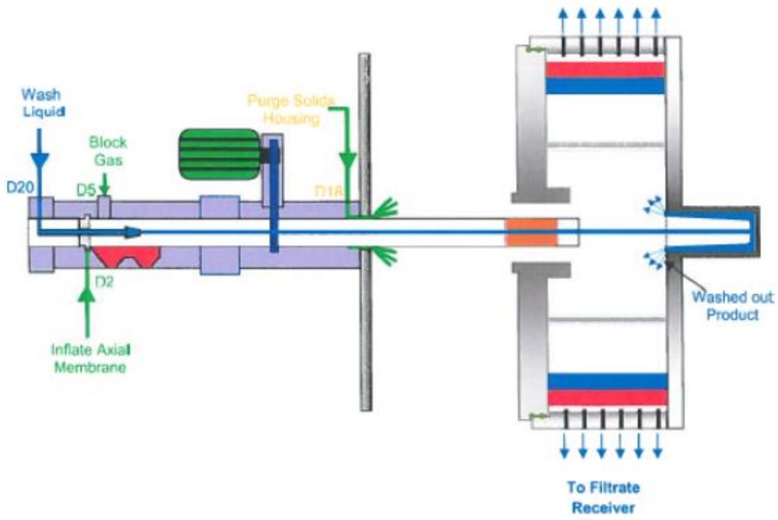

Figure 36 Section of centrifuge dryer during technical wash [31]

<u>Normal wash</u>

After the technical wash, a normal wash with the first solvent is done. Again, the amount of washing solvents resets to 0 at the start of the normal wash. The washing solvent is applied on the cake using the feed pipe, as shown in Figure 30. This ensures that any residue in the feeding pipe is washed down onto the filter cake, to minimize yield loss. The washing solvent flows from the pressurized washing tank D0XX-T011 (XX equal to number of dryer), or pressurized wash container, via the feeding pipe onto the rotating filter cake. This pathway is shown in Figure 37. The orange color in Figure 37 is the pathway from the washing tank to the centrifuge dryer. The green color is the pathway from the washing container to the centrifuge dryer.

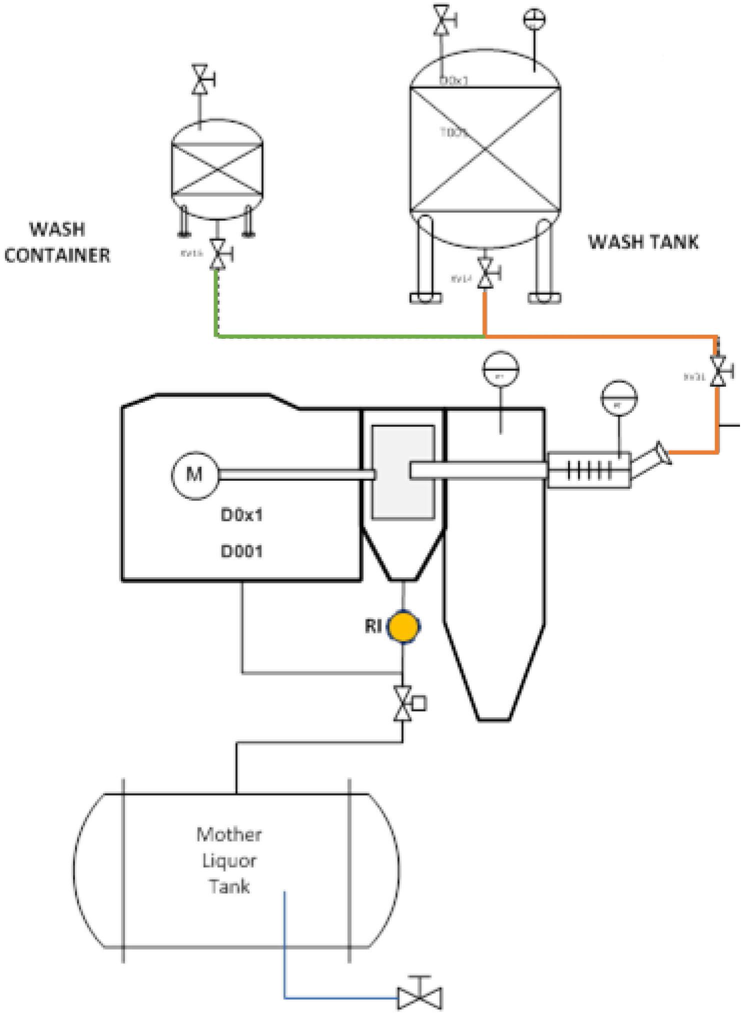

Figure 37 Process diagram of centrifuge dryer, washing tank, washing container and mother liquor tank [32]

Applying the washing solvent can be done in 2 ways:

- Normal washing
- Stepped washing

In normal washing the set amount of washing solvent is applied on the cake in 1 go, as shown in Figure 38. In stepped washing the washing solvent is added in steps, as shown in Figure 39. Only when an increase in amount of washing solvent is measured, washing solvent is added to the filter cake. The addition of the washing amount in steps allows the excess liquid to drain from the filter cake. Step washing is mostly done when highly compressible with a high resistance are washed. The increased resistance could cause the washing liquid to accumulate on the filter cake, causing liquor load and thus unbalance in the centrifuge dryer. Unbalance of the centrifuge could lead to tremors and damage of the centrifuge.

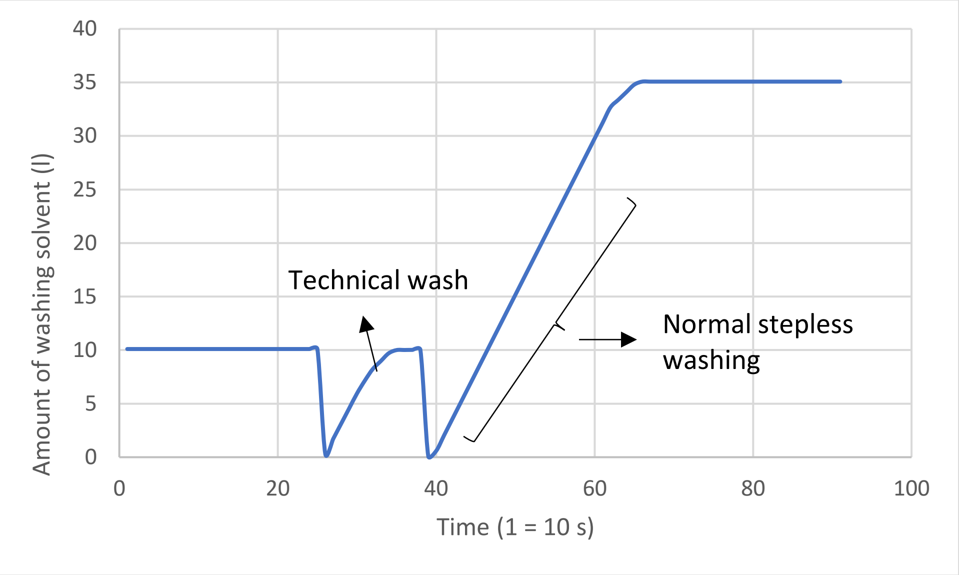

Figure 38 Washing trend example of normal or stepless washing

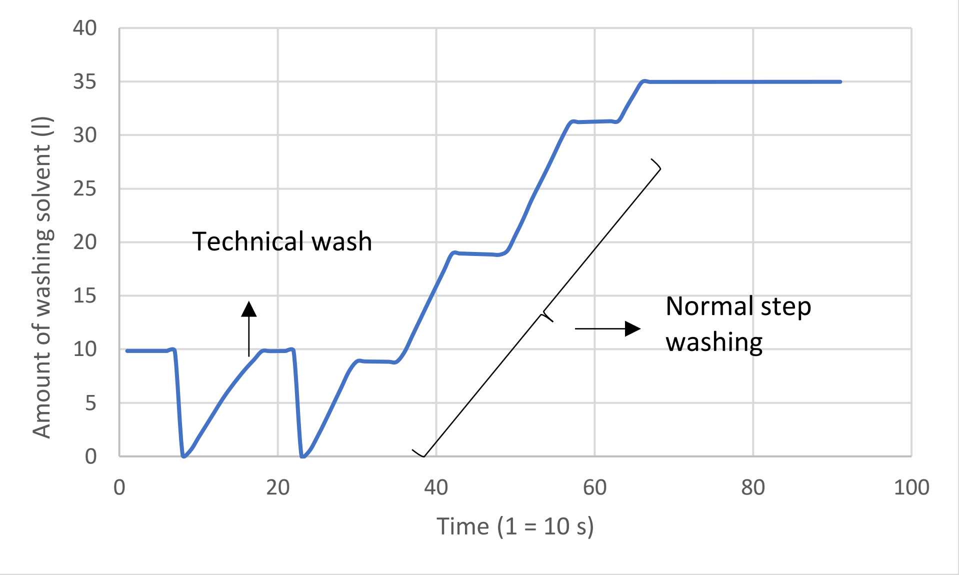

Figure 39 Washing trend example of step washing

<u>Multiple solvents wash</u>

After the first normal wash, a second wash with a second washing solvent can be done, as shown in Figure 40. The use of a second washing solvent could be done to increase the efficiency of downstream processing, such as drying of the filter cake. The displacement of the first washing solvent with a second solvent was previously discussed in (2.3.5.3).

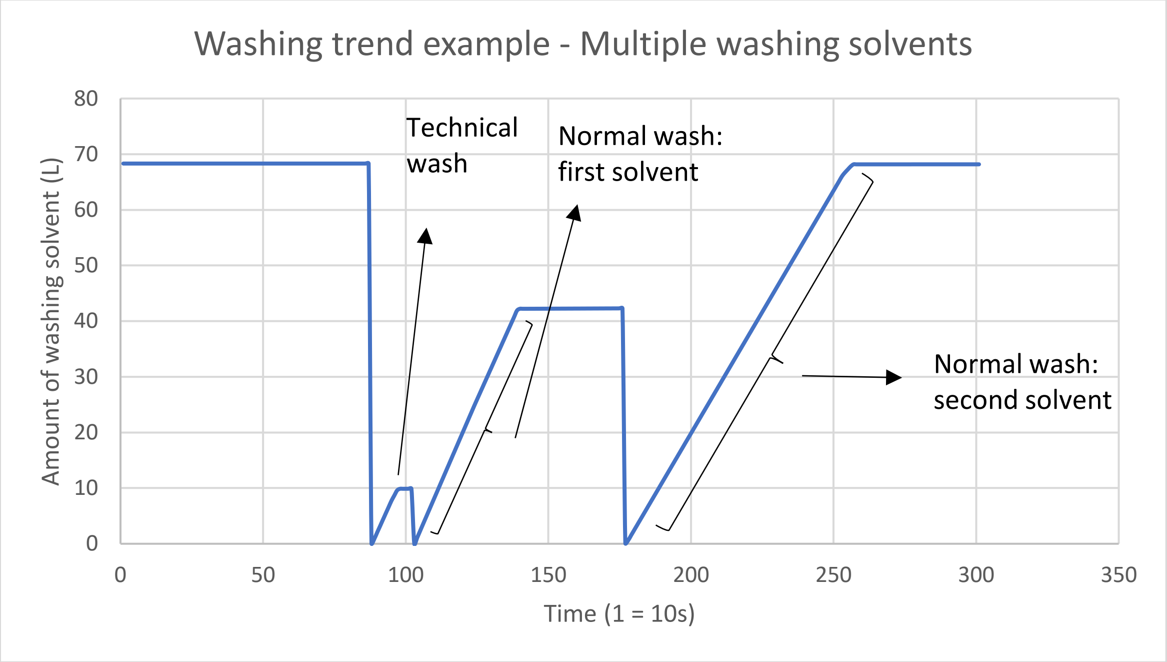

Figure 40 Washing trend example of normal wash with multiple washing solvents

After washing is complete the filter cake is spun at a set rotational speed to remove any excess liquor.

3.3.1.3. PAC

As said earlier, after washing is complete the filter cake is spun at a set rotational speed to remove any excess liquor. Pressure added centrifugation (PAC) is used to deliquor the cake even further. A schematic view of the PAC process is shown in Figure 41.

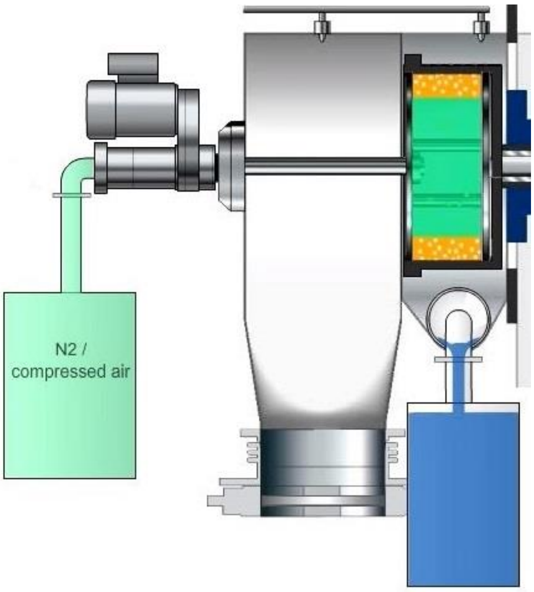

Figure 41 PAC process, schematic overview [17]

The centrifuge dryer is brought to a pressure of 6 bar, using a N_2 flow. Any excess liquid remaining in the cake is removed under the influence of the pressure difference. After a certain time period, or after a set amount of liquid is collected, the PAC step is finished.

3.3.1.4. Drying

The cake is dried using a N_2 flow. This N_2 flow can be heated or cooled to a desired temperature using a heat exchanger. The N_2 flow passes through the cake, removing excess liquor, increasing dryness of the cake. Figure 42 shows a schematic overview of the deliquoring of the cake during the drying process.

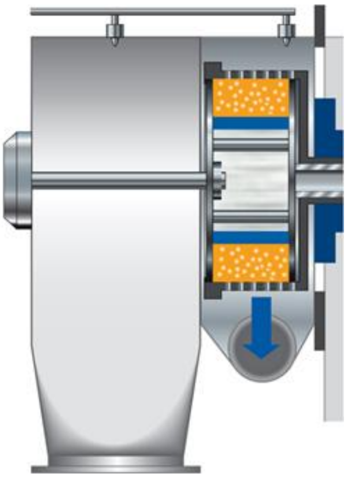

Figure 42 Deliquoring of the cake during the drying process, schematic overview [17]

3.3.1.5. Discharge

Ejecting of the cake is done after washing or drying of the cake as the filter cake can be ejected dry or wet. The cake is ejected from the centrifugal filter using an inverting filter screen mechanism. This mechanism is discussed in 2.4.2. The filter cake is ejected to the ground floor, where the product is packaged in the assigned recipient. Figure 43 shows a schematic overview of the discharge of the filter cake using the inverting filter screen mechanism.

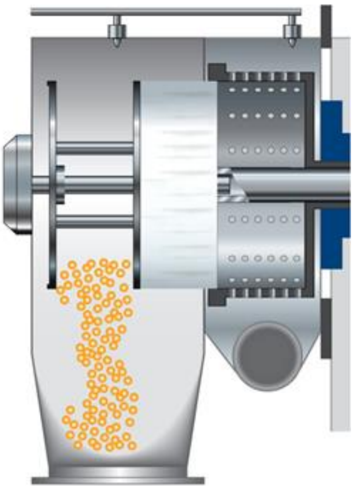

Figure 43 Discharge of the filter cake using an inverting filter screen mechanism, schematic overview [17]

3.3.1. Lab testing

The refractive index value depends on the medium, temperature and concentration, as discussed in 2.5. The influence of temperature, API conc in washing solvent, washing solvent ratio and evaporation on the refractive index were all tested on lab scale. Refractive indexes were measured using the refractometer PR-23.

3.3.1.1. Influence of temperature

Since the refractive index is influenced by the temperature, the exact influence of the temperature for each used washing solvent on the refractive index is tested. The washing solvents that were tested are given in Table 13.

Table 13 Washing solvents that were tested on influence of temperature on the refractive index and their according products

Washing solvent	Product
Ethanol	$NaHCO_3$
Methanol	$NaHCO_3$
Methyl Ethyl Ketone (MEK)	RSV678 Crude / Not milled
IPAc / Heptane (1:4 vol)	Alios T3728
Acetonitrile / Water (1:2.5 vol)	Alios T3730
Acetonitrile / Water (1:4 vol)	Alios Crude

The refractive index of the washing solvent was measured at 4 different temperature points. The temperature points are 5, 15, 20 and 25°C. These are the working temperatures of the centrifuge dryer at the CDPP. Since evaporation of the solvents mixture posed a problem, no temperatures above 25°C were measured. The washing solvents were cooled using an ice bath until the lowest temperature. All recipients were covered during testing to prevent additional evaporation.

3.3.1.2. Influence of API concentration in washing solvent to RI

The refractive index measures the concentration in the solvent that passes. The washing solvents are selected in a way that very little or no product would dissolve into the solvent. Although the solubility into the washing solvent is very low, the change in concentration could still affect the refractive index. This effect was tested in the lab by dissolving the product into their according washing solvent until max solubility. The products that were tested and their solubility are given in Table 14.

Table 14 Products tested on influence of API concentration in washing solvent on refractive index and the solubility of those products in their respective washing solvents

Product	Washing solvent	Solubility (g/l)
Alios T3728	IPAc / Heptane (1:4 vol)	0.8
Alios T3730	Acetonitrile / Water (1:2.5 vol)	2.3

Alios Crude	Acetonitrile / Water (1:4 vol)	1.9

The solubility of the products was not known at the time of the tests. A set amount of product was dissolved into the washing solvent and the refractive index was measured. After the refractive index was measured, the amount of product in the washing solvent was increased. This process was repeated until 1 g/l or the maximum solubility was reached. If max solubility was reached, the product was let to precipitate. The washing solvent above the solid product was than measured on the refractometer. In total, including the blank, 5 concentrations were measured. Since all products are expensive, only small quantities of products were used to conduct the tests. All solutions were made in 10 ml vials.

3.3.1.3. <u>Influence of washing solvent ratio to RI</u>

The refractive index is dependent of the medium. Any change in solvent mixture ratio would affect the refractive index of that mixture. Solvent mixtures are mixed on site. On each individual volume of the washing solvent, an error of 5% is permitted. The products that use a mixture of solvents as a washing solvent are given in Table 15.

Table 15 Washing solvents tested for influence of solvent ratio on the refractive index and their according products

Washing solvent	Product
IPAc / Heptane (1:4 vol)	Alios T3728
Acetonitrile / Water (1:2.5 vol)	Alios T3730
Acetonitrile / Water (1:4 vol)	Alios Crude

Only the Alios products were tested on the influence of solvent ratio, as they use a mixture of solvents as a washing solvent. Other products, such as RSV678 and Orexin, use pure solvents as washing solvents and will not be influenced by this effect. For each washing solvent 5 washing solvent ratios are tested. The washing solvent ratios that were tested for IPAc/Heptane are 1:3, 1:3.5, 1:4, 1:4.5 and 1:5 vol. The washing solvent ratios that were tested for Acetonitrile/water are 1:1.5, 1:2, 1:2.5, 1:3, 1:3.5, 1:4, 1:4.5 and 1:5 vol.

The refractive index of the pure solvents are given in Table 16.

Table 16 Refractive indexes of the pure washing solvents that are tested

Washing solvent	Refractive index at 20°C
IPAc	1.377
Heptane	1.387
Acetonitrile	1.344
Water	1.333

3.3.1.4. <u>Influence of evaporation</u>

The washing solvents mixtures refractive index changed constantly during tests on room temperature. Since organic solvents are used as washing solvents, evaporation was a problem.

Therefore, the influence of evaporation of the washing solvents mixtures on the refractive index was tested. The washing solvents and their corresponding products that were tested are given in Table 17.

Table 17 Washing solvents that were tested on influence of evaporation on the refractive index and their according products

Washing solvent	Product
IPAc / Heptane (1:4 vol)	Alios T3728
Acetonitrile / Water (1:2.5 vol)	Alios T3730
Acetonitrile / Water (1:4 vol)	Alios Crude

The washing solvents were measured with the refractometer and left on the probe for 5 min. The refractive index was measured at 0, 10, 20, 30, 60, 120, 240 and 300 s. The washing solvents mixtures were exposed to room temperature of 21°C.

3.3.2. Pilot tests

This paragraph discusses the influence of process parameters, with the exception of temperature, on the washing curves. The tests, excluding temperature testing, are executed using a $NaHCO_3$ filter cake. All tests were executed in the pilot plant using centrifuge dryer D041 (Figure 21), which is explained in detail in 3.2.1. Refractive indexes are measured using the PR-23 (3.2.2) and data is collected using PI (3.2.3). The tests were executed before my intern period.

3.3.2.1. Washing solvent flow time

The time between washing tank and refractometer through the centrifuge dryer was tested. The pathway is shown in Figure 37. Water at 21.4°C is used as a washing solvent. No filter cake is used. The time between start of washing and first change in refractive index is measured. The process parameters are given in Table 18. IBW is short for industrial used water.

Table 18 Process parameters used in the testing the washing solvent flow time from wash tank to refractometer

Process parameter	Wash with IBW from washing tank
Cake	No cake used
Dryer used	D041
Washing solvent	IBW
Washing amount (l)	25
Temperature washing solvent in wash tank(°C)	21.4

The washing trends were measured using the refractive index. The data from the washing trends was trended in PI.

3.3.2.2. Temperature

The influence of the temperature on the refractive index is tested using water as a washing solvent. No $NaHCO_3$ was used as a filter cake. Not using a filter cake allowed for smooth testing of the influence of temperature on the refractive index. Since filter cakes could have a low solubility in the washing solvent, influencing the refractive index. Water heated to 50°C is used as a washing solvent.

The washing parameters used for this test are summarised in Table 19. IBW is short for industrial used water.

Table 19 Process parameters used in the testing the influence of temperature of the washing solvent on the refractive index

Process parameter	**Wash with IBW from washing tank**
Cake	No cake used
Dryer used	D041
Washing solvent	IBW
Washing amount (l)	40
Temperature washing solvent in wash tank(°C)	49.3

The washing trends were measured using the refractive index. The data from the washing trends was trended in PI.

3.3.2.3. Rotation speed of filtering centrifuge

To test the influence of the rotational speed of the filtering centrifuge on the wash time of a filter cake, a $NaHCO_3$ filter cake of 4 cm was used. 25 kg of $NaHCO_3$ was brought into suspension in 250 L of ethanol as a mother liquor. This suspension slurry was fed to the centrifuge dryer. The filter cake is first washed at 500 RPM. The wash consists out 2 solvents using a solvent switch. Firstly the filter cake is washed with 45 L of ethanol and then the cake is washed with an additional 42 L of ethanol for a total of 87 L. After this wash, the RPM speed is increased from 500 to 800 RPM. The washing with both solvents is repeated. This time 36 L of ethanol and 38 L of methanol is used for a total of 74 L. The filter cake was not changed in-between tests as $NaHCO_3$ is non- soluble in ethanol and poorly soluble in methanol (2.13 wt%). The process parameters of the 2 washes are shown in Table 20.

Table 20 Process parameters used in the testing the influence rotational speed of the filtering centrifuge on the washing trends

Process parameter	Ethanol-methanol wash at 500 RPM	Ethanol-methanol wash at 800 RPM
Reactor		
Reactor used	R043	R043
Product	$NaHCO_3$	$NaHCO_3$
mass product in reactor (kg)	25	25
Mother liquor	Ethanol	Ethanol
Amount of mother liquor (L)	250	250
Cake		
Cake thickness (cm)	4	4
Dryer used	D041	D041
Wash		
FV03	5%	25%
Washing solvent 1	Ethanol	Ethanol
Washing amount 1 (L)	45	36
Washing solvent 2	Methanol	Methanol
Washing amount 2 (L)	42	38
Total washing amount (L)	87	74
Centrifuge speeds (RPM)	**500**	**800**
Temperature washing solvent in wash tank (°C)	24.6	24.6

3.3.1. Washing curves

The washing curves of Alios T3728, Alios T3730 and Alios Crude will be examined. The curves will be compared for deviations and effects. Of each product, a golden batch will be selected. This golden batch is the batch with the least deviations. The process parameters after the golden batch will also remain constant. The relevant process parameters of the washing process will be discussed in 4. Results and discussion. All products were filtered and washed within the centrifuge dryer discussed in 3.2.1. The refractive index was measured using refractometer PR-23, which is discussed in detail in 3.2.2. All data was collected and studied using OSIsoft processbook PI and excel.

4. Results and discussion

4.1. Lab tests

Refractive index as process analytical technology is a new technique. Hence why the influence of process parameters on the refractive index are not known. Lab tests were done to test the influence of temperature, concentration of API in washing solvent, washing solvent ratio and evaporation. The results of these test will be discussed prior to the washing curves measured in the CDPP.

4.1.1. Influence of temperature

The refractive index value depends on the medium, temperature and concentration, as discussed in 2.5. The refractometer PR-23 by Elscolab has a built-in temperature compensation, shown in (4.1). [33]

$$+1°C \leftrightarrow -0.0001\, nD \tag{4.1}$$

However, this temperature compensation is not liquid specific. The temperature compensation of Elscolab is based on water. The temperature of organic solvents and mixtures of solvents could have a larger or smaller effect on the refractive index. During the tests al parameters, except for the temperature, were held constant. The refractive index is inversely proportional to the temperature, as given by (4.1). A linear trend will be plotted through the 5 tested temperature points.

A trend of the results of ethanol is given in Figure 44.

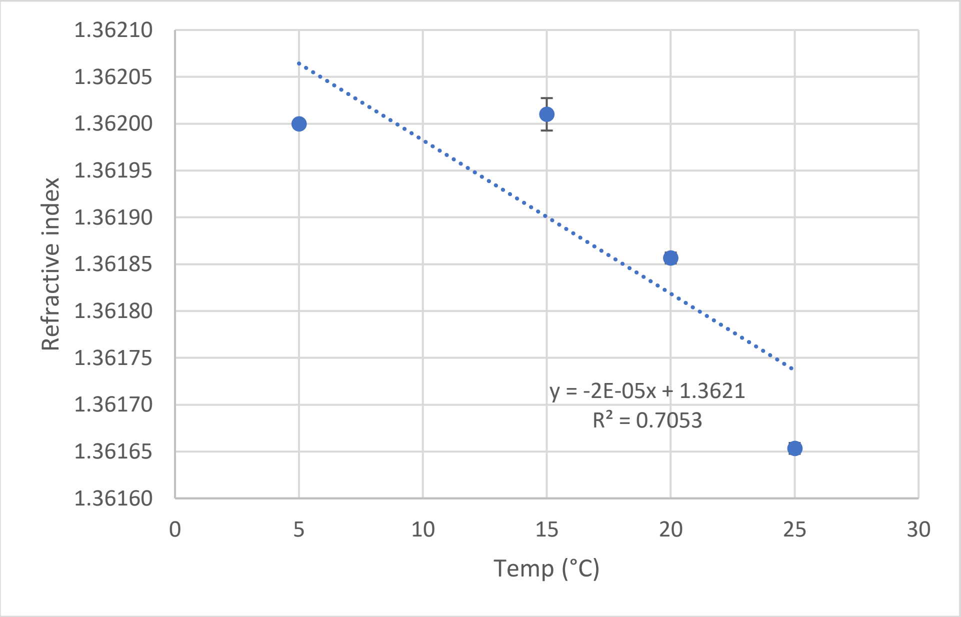

Figure 44 Influence of temperature on refractive index for the washing solvent ethanol

From each linear curve, the gradient is the dependency of the refractive index to the temperature. The temperature dependency for each solvent is given in Table 21.

Table 21 Influence of temperature on refractive index trend lines of washing solvents

Washing solvent	Trend gradient	Correlation R^2
Ethanol	-1.638E-05	0.705
Methanol	-1.758E-05	0.700
Methyl Ethyl Ketone (MEK)	-2.109E-05	0.668
IPAc / Heptane (1:4 vol)	-2.066E-05	0.701
Acetonitrile / Water (1:2.5 vol)	-1.771E-05	0.897
Acetonitrile / Water (1:4 vol)	-1.456E-05	0.997

The correlation of the solvents ethanol, methanol, MEK, IPAc/Heptane are low. This low correlation is due to the evaporation of the solvents during testing. During the measurements, the refractive index kept changing. Evaporation of the solvent caused a change in temperature, resulting in a change in refractive index. For the solvents mixture, not only the temperature changed, but also the solvent ratio of the mixture. The effect of evaporation will be discussed in 4.1.4.

From the trend lines the gradient indicates how much the refractive index will change when increasing the temperature by 1°C. For example, increasing the temperature of ethanol by 1°C will result in a decrease of -0.00001638 in the refractive index, as shown in (4.2).

$$Ethanol\colon 1°C \ \leftrightarrow - 0.000016\, nD \tag{4.2}$$

The influence of temperature on the refractive index using organic solvents or solvents mixtures is very small. Given the accuracy of the used refractometer PR-23 is only ±0.0002, only a large change in temperature, of at least 10°C, would be noticeable in the measurements of the refractive index. Further in this research the temperature effect on the refractive index of water will be used.

4.1.2. Influence of API concentration in washing solvent

The washing solvents are selected in a way that very little or no product would dissolve into the solvent. Although the solubility into the washing solvent is very low, the change in concentration could still affect the refractive index. This effect was tested in the lab by dissolving the product into their according washing solvent until max solubility. The products that were tested are given in Table 22.

Table 22 Solubility of products into washing solvents

Product	Washing solvent	Solubility (g/l)
Alios T3728	IPAc / Heptane (1:4 vol)	0.8
Alios T3730	Acetonitrile / Water (1:2.5 vol)	2.3
Alios Crude	Acetonitrile / Water (1:4 vol)	1.9

Since the solubility of the products was not known at the time of the lab tests, a set amount of product was dissolved into the washing solvent. The amount of product into the washing solvent was increased until the product no longer dissolved. At this point, the max solubility of the product into the washing solvent was reached. If the max solubility of the product was reached, as in Alios T3728, the solid particles were let to settle. The solvent above the precipitated solid product was measured on the refractometer. The results are given in Figure 45, Figure 46 and Figure 47. The max solubility is given by a vertical red line.

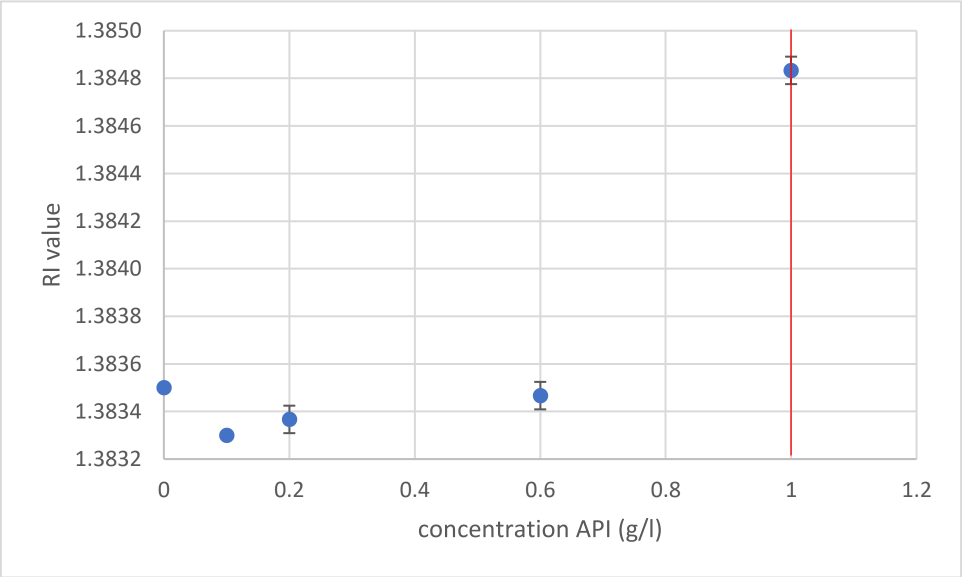

Figure 45 Influence of API concentration of Alios T3728 in IPAc/Heptane (1:4 vol) on refractive index

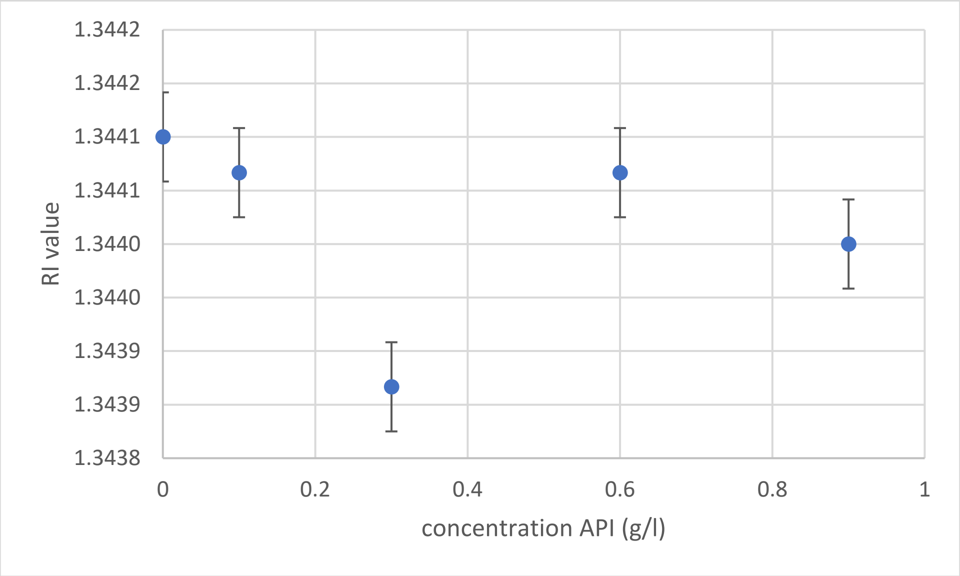

Figure 46 Influence of API concentration of Alios T3730 in Acetonitrile/Water (1:2.5 vol) on refractive index

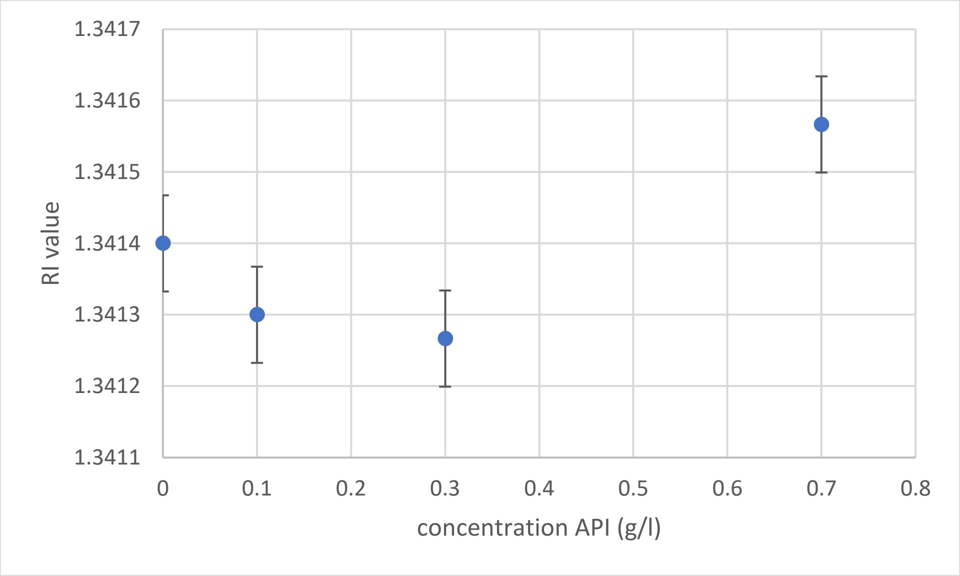

Figure 47 Influence of API concentration of Alios T3730 in Acetonitrile/Water (1:4 vol) on refractive index

No correlation between the API concentration in the washing solvent and the refractive index was detected. Any recorded changes in refractive index were too small to be considered significant. Changes in refractive index of 0.0002 for Alios T3730 and Alios Crude were measured while increasing the concentration of dissolved API in the washing solvent. These changes can be discarded as the accuracy of the refractometer is ±0.0002. The error on the measurements were also in the same order of magnitude as the changes in refractive index.

Opposite to the small changes of 0.0002 for Alios T3730 and Alios Crude, is the change of 0.0013 in refractive index for Alios T3728. This increase in refractive index was measured between the points of 0.6 g/l and 0.8 g/l. No change in refractive index for the lower concentration was detected. Concluding that the measurement for the max concentration can be discarded.

The tests conclude that the API concentration in the washing solvent has no effect on the refractive index. In theory, the refractive index should increase with increasing concentration. Since the solubility of the product in the washing solvent and the accuracy of the refractometer were to small, no effect could be detected. Further testing should be done to determine the influence of API concentration in the washing solvent on refractive index, for each product.

4.1.3. Influence of washing solvent ratio

Instead of using a pure solvent as a washing solvent, a mixture of 2 solvents can also be used. The mixtures are made in the washing tank by adding the correct amount of pure washing solvent. The solvents are constantly mixed inside the tank. During the addition of the washing solvents an error of 5% on the volume is permitted. Since the refractive index depends on the medium, the refractive index will be influenced by the ratio of the pure solvents. The results of the influence of this solvent ratio on the refractive index are discussed below.

The refractive index of the pure solvents are given in Table 23.

Table 23 Refractive indexes of the pure washing solvents that are tested

Washing solvent	Refractive index at 20°C
IPAc	1.377
Heptane	1.387
Acetonitrile	1.344
Water	1.333

Since the effect of the ratio of the washing solvent is solvent specific, the results are discussed per washing solvent in 4.1.3.1, 4.1.3.2 and 4.1.3.3.

4.1.3.1. Alios T3728

The product Alios T3728 is washed with a mixture of IPAc and Heptane. The mixture has a 1:4 volume ratio. The results are shown in Figure 48. The grey and orange horizontal line are the refractive indexes of Heptane and Isopropyl Acetate. A linear trend of the refractive index values is given in yellow.

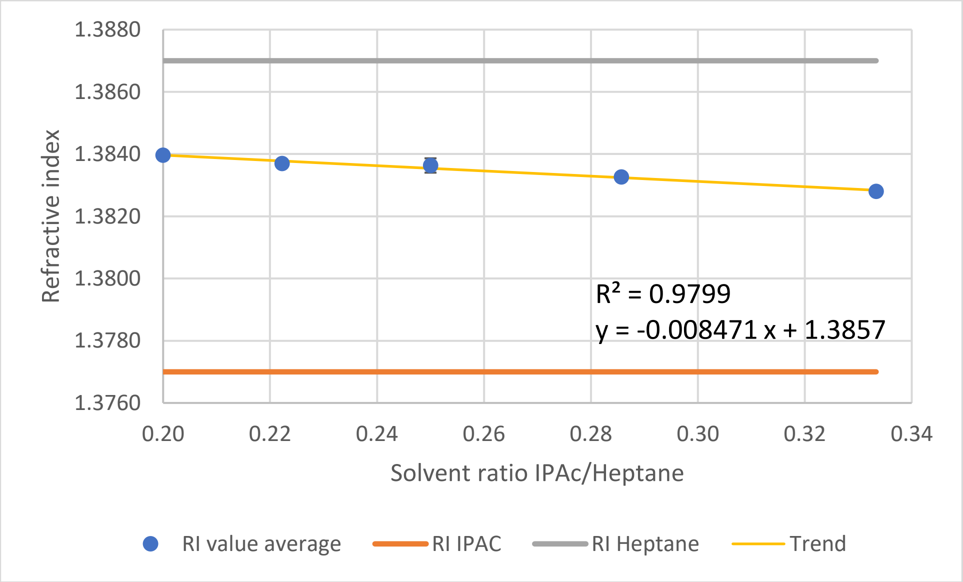

Figure 48 Influence of solvent ratio on refractive index - washing solvent IPAc/Heptane (1:4 vol)- RI values pure washing solvent

The chart shows that the refractive index of the solvent mixture decreases as the ratio of IPAc to heptane increases. This decrease in refractive index is to be expected as the refractive index of pure IPAc is lower than the mixture and pure Heptane. Figure 48 clearly show the decrease of the refractive index of the solvent mixture towards the refractive index value of pure IPAc of 1.377.

4.1.3.2. Alios T3730

The product Alios T3730 is washed with a mixture of Acetonitrile and water. The mixture has a 1:2.5 volume ratio. For the solvent mixture acetonitrile/water (1:2.5 vol) an increase in refractive index for increasing solvent ratio is measured. The results are shown in Figure 49.

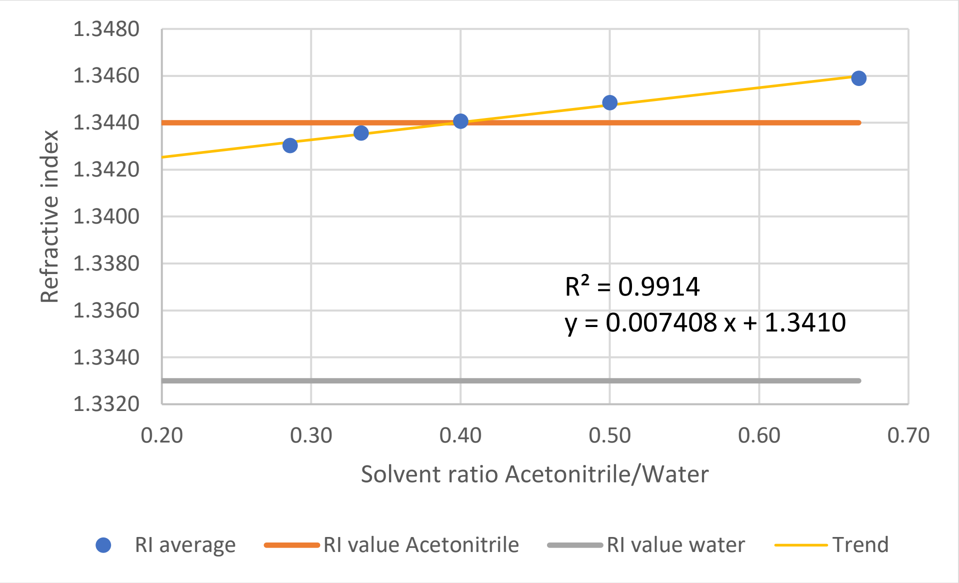

Figure 49 Influence of solvent ratio on refractive index - washing solvent Acetonitrile/water (1:2.5 vol)- RI values pure washing solvent

4.1.3.3. Alios Crude

The product Alios Crude is washed with a mixture of Acetonitrile and water. The mixture has a 1:4 volume ratio. For the solvent mixture Acetonitrile/water (1:4 vol) an increase of refractive index for increasing solvent ratio is measured. The results are shown in Figure 50.

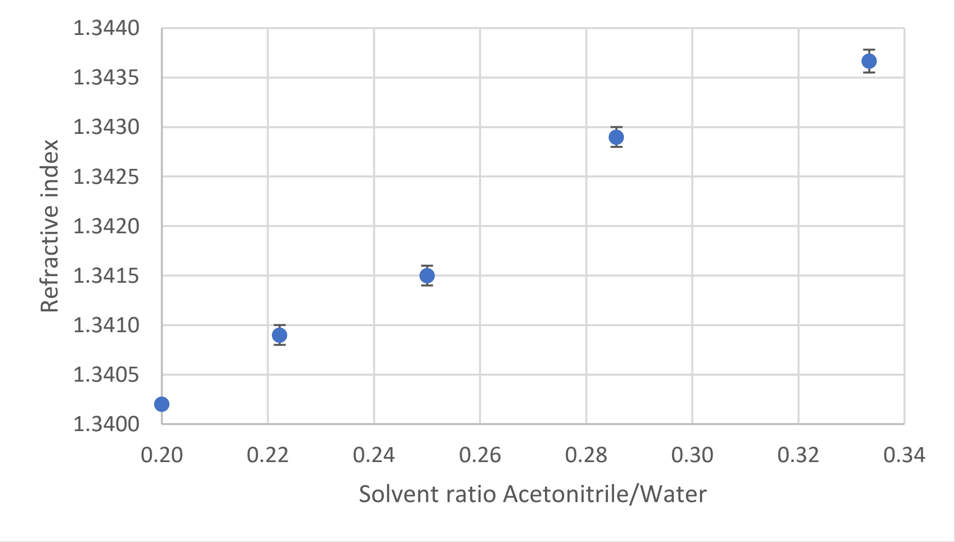

Figure 50 Influence of solvent ratio on refractive index - washing solvent Acetonitrile (1:4 vol)

The effect of the solvent ratio on the refractive index is again as expected with a linear correlation coefficient of 0.9803 as shown in Figure 51. The refractive indexes of the pure washing solvents are added to the chart in Figure 51. A linear trend is also calculated and plotted on this chart.

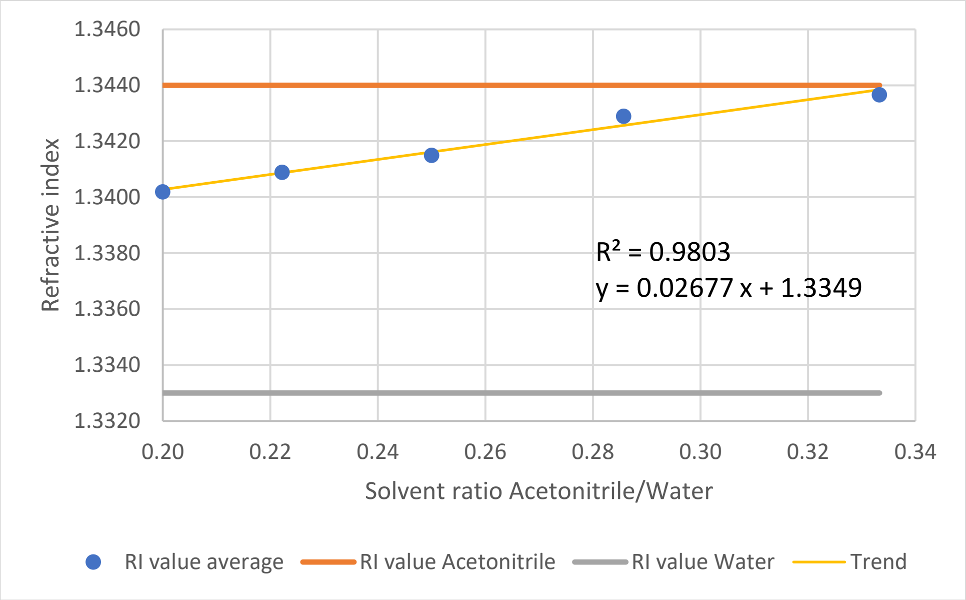

Figure 51 Influence of solvent ratio on refractive index - washing solvent Acetonitrile/water (1:4 vol)- RI values pure washing solvent

Figure 51 clearly shows the increase of the refractive index of the solvent mixture towards the refractive index value of pure Acetonitrile of 1.3440.

4.1.3.4. Trend

Of all solvent mixtures a linear trend line was plotted to calculate the effect of the solvent ratio on the refractive index. Table 24 shows the linear trend functions and their gradients for each mixture of washing solvent.

Table 24 Linear trend functions for each washing solvent of the influence of solvent ratio on the refractive index

Washing solvent	Linear trend function	Gradient	Correlation R^2
IPAc/Heptane (1:4 vol)	y = -0.008471 x + 1.3857	-0.008471	0.9799
Acetonitrile/Water (1:2.5 vol)	y = 0.007408 x + 1.3410	0.007408	0.9914
Acetonitrile/Water (1:4 vol)	y = 0.02677 x + 1.3349	0.02677	0.9803

The influence of the solvent ratio on the refractive index is a linear effect that is unique for each mixture of washing solvents. Increasing the ratio of one of the washing solvents in the mixture, causes the refractive index to increase or decrease towards the refractive index of the pure washing solvent, as shown in (4.3).

$$RI = -0.008471 * Solvent\ ratio + 1.3857 \tag{4.3}$$

The gradient determines the significance of the change in the refractive index. The intercept is approximately equal to the refractive index value of the pure washing solvent.

During the mixing of the pure solvents, to create the washing solvent mixture, a fault of 5% on the volume is permitted. Using the washing solvent mixture IPAc/Heptane as an example we become the following results. A volume of 100 L IPAc and 400 L Heptane was used for calculation. The refractive index was calculated using the linear function from Table 24. The calculated refractive index values are shown in Table 25.

Table 25 Calculated refractive index values for 5% error on the volume of washing solvent IPAc/Heptane

Solvent volume (IPAc/Heptane)	**Solvent ratio (IPac/ Heptane)**	**Refractive index value**
100 L IPAc 400 L Heptane	0.25	1.38358
Change in volume of IPAc		
95 L IPAc 400 L Heptane	0.2375	1.38369
105 L IPAc 400 L Heptane	0.2625	1.38348
Change in volume of Heptane		
100 L IPAc 380 L Heptane	0.2632	1.38347
100 L IPAc 420 L Heptane	0.2381	1.38368
Change in volume of IPAc and Heptane		
95 L IPAc 420 L Heptane	0.2262	1.38374
105 L IPAc 380 L Heptane	0.2763	1.38332

The permitted fault in volume when making the washing solvent mixture causes a change in the refractive index value. The max error in refractive index value, for a 5% error in volume, is 0.016%. The error of the refractive index values for the other solvents are shown in Table 26.

Table 26 Refractive index error of washing solvents due to 5% error in volume of washing solvent

Washing solvent	Refractive index error (%)
IPAc/Heptane (1:4 vol)	0.016
Acetonitrile/Water (1:2.5 vol)	0.023
Acetonitrile/Water (1:4 vol)	0.052

The error in refractive index is small for all washing solvents. However, washing processes that have a small change in refractive index during the washing process could be influenced by this effect.

4.1.4. Influence of evaporation

The solvent ratio of the washing solvent has a large effect on the refractive index, as discussed before in 4.1.3. The refractometer PR-23 is mounted between the centrifuge dryer and the mother liquor tank, as show in 3.2.2 on Figure 27.

When the filter cake is washed with the washing liquor a high solvent flow over the refractometer will cause a signal. The refractive index of the passing liquid is measured. However, when the washing of the filter cake stops, the flow of the liquid passing over the refractometer decreases. Since the refractometer PR-23 is mounted with a siphon. The washing solvent is trapped until new washing solvent is provided, or the washing solvent evaporates.

During pressurized advanced centrifugation (PAC) the pressure on the filter compartment is increased to 6 bar. During this process there is a flow of N_2 over the refractometer from the filter compartment to the mother liquor tank. This flow of N_2 increases the evaporation rate of any solvent left on the refractometer.

For some products, a mixture of solvents is used as a washing solvent. These solvents are not equally volatile. Evaporation of the more volatile solvent in the mixture could happen, changing the ratio of the washing solvent. The vapour pressure of each pure solvent is given in Table 27.

Table 27 Vapour pressure of pure solvents

Washing solvent	Vapour pressure (kPa) at 20°C
IPAc	6.27
Heptane	4.80
Acetonitrile	9.71
Water	2.30

The product Alios T3728 is washed with a mixture of IPAc and Heptane. The mixture has a 1:4 volume ratio. The results are shown in Figure 52. The refractive indexes of the pure washing solvents are given in grey and orange for Heptane and IPAc respectively. A linear trend is plotted in yellow.

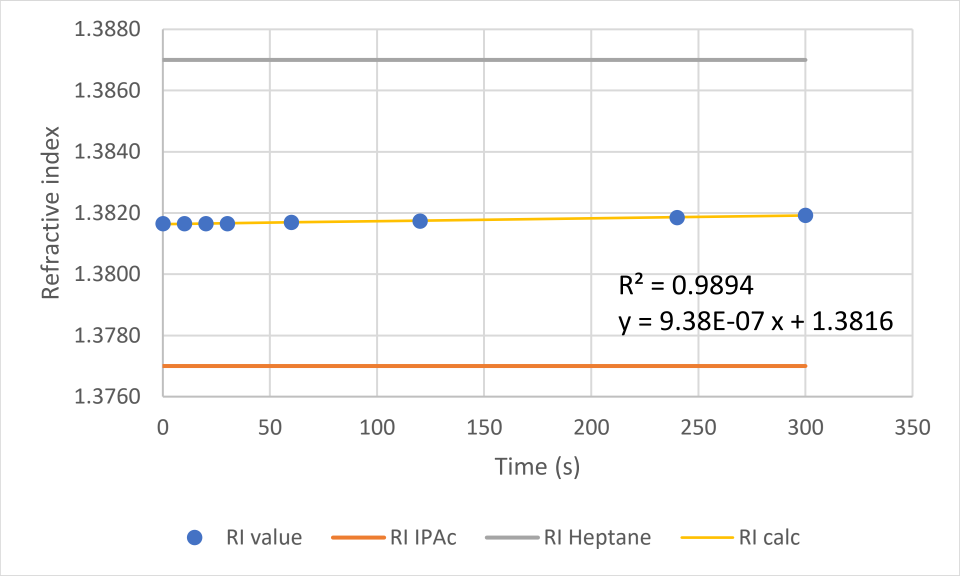

Figure 52 Influence of evaporation of IPAc/Heptane (1:4 vol) on the refractive index

The refractive index stays steady during the first 30 seconds of the test. After 30 seconds the refractive index starts to slowly increase towards the refractive index value of pure Heptane. IPAc is more volatile than Heptane and evaporates faster than Heptane, changing the solvent ratio of the mixture. The increased ratio of Heptane changes the refractive index of the mixture towards the refractive index of pure Heptane.

The steady state of the refractive index during the first 30 seconds of the test are also measured with the solvent mixture Acetonitrile/Water (1:2.5 vol) and Acetonitrile/Water (1:4 vol). This steady state

The refractive index of the mixture during the test shifted towards the refractive index of the pure solvent that was the least volatile of the two. This effect was observed in all tested solvents.

The linear trends and their correlation of the solvent mixtures are given in Table 28.

Table 28 Evaporation linear trends and correlation for washing solvents

Washing solvent	Linear trend function	Correlation R²
IPAc/Heptane (1:4 vol)	y = 9.38E-07 x + 1.3816	0.9894
Acetonitrile/Water (1:2.5 vol)	y = -3.36E-06 x + 1.3425	0.9950
Acetonitrile/water (1:4 vol)	y = -7.11E-06 x + 1.3405	0.9771

The gradient of the curve is the change in refractive index per second. Again, the effect of evaporation on the refractive index is small. To measure the extent of the influence an example calculation is done below.

The time between processes can vary from 1 up to 30 min. A time of 5 min is chosen for the calculation of the effect of evaporation on refractive index. The calculated refractive index error is given in Table 29.

Table 29 Calculated evaporation error on refractive index

Washin solvent	Refractive index error
IPAc/Heptane (1:4 vol)	0.000281
Acetonitrile/Water (1:2.5 vol)	-0.001008
Acetonitrile/water (1:4 vol)	-0.002133

The effect of evaporation on the refractive index over a period of 5 min is still small. However, in washing processes were the change in refractive index is small, this could influence the measurement. Evaporation should always be considered at the end of the washing process. During Advanced Pressurized Centrifugation (PAC) evaporation has a larger effect on the refractive index since the N_2 flow causes a faster evaporation of the volatile solvent in the mixture. When PAC commences an increase or decrease in refractive index could be detected, caused by evaporation of the volatile washing solvent in the mixture. This effect only occurs when mixtures of washing solvents are used.

4.2. Pilot Tests

In this paragraph all tests were done in the CDPP plant. All tests were done on centrifuge dryers, which are described in 3.2.1. The refractometer PR-23 was used to measure the refractive index. Specific parameters and operations of the refractometer are discussed in detail in 3.2.2.

4.2.1. Washing solvent flow time

The flow time of the washing solvent from washing tank to the refractometer was tested. This test was done to achieve additional process knowledge about the centrifuge dryer system. The results are shown in Figure 53. The refractive index is given on the left y-axis and shown in orange. The amount of washing solvent is given on the right y-axis and shown in blue on the graph. Both variables are plotted against the time. The drop in washing amount shows the start of the feeding of the washing solvent. The amount of washing solvent resets from this point. The amount of washing solvent that is added after the reset is the amount that is added to the centrifuge dryer, which is 25.8 L of water.

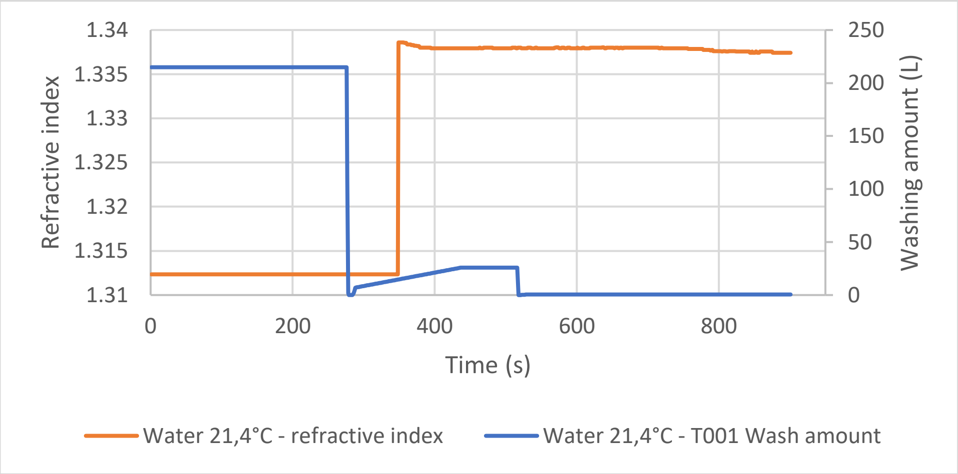

Figure 53 Influence of temperature on refractive index - Time of washing solvent from tank to refractometer

The time spend from washing tank, through the centrifuge dryer, to the first measurement of the refractive index is calculated below in (4.4).

$$\Delta t = |t_1 - t_2| = |276\ s - 352\ s| = 76\ s \qquad (4.4)$$

The time from the washing tank to the refractometer without any filter cake is 76 s.

4.2.2. Influence of temperature

To test the influence of the temperature of the washing solvent on the refractive index, test were performed without a filter cake. Water at 50°C was used as a washing solvent. The refractometer is equipped with a temperature sensor to measure the temperature of the passing solvent. The results of the test are given in Figure 54. On the left y-axis the amount of washing solvent is given in blue. On the right y-axis the temperature is given in red. Both variables are plotted against the time.

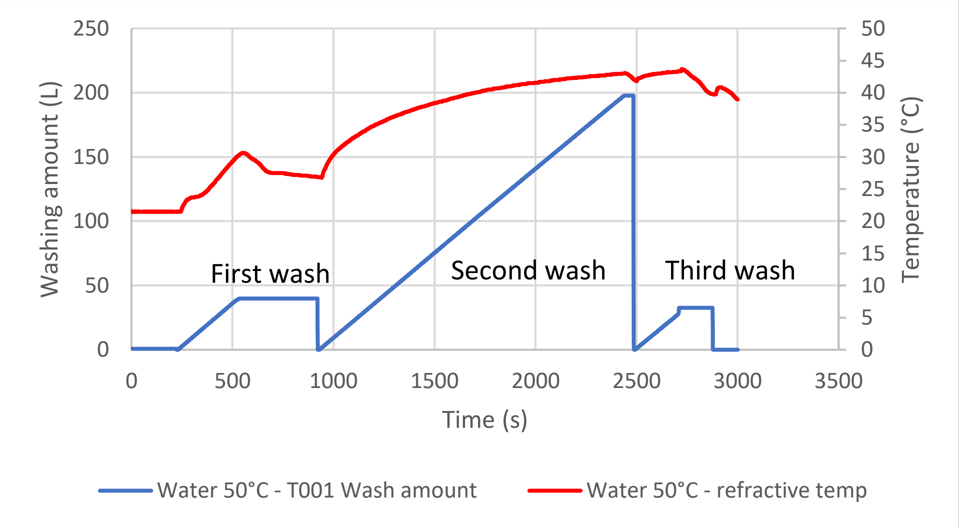

Figure 54 Changes of temperature of the refractometer during first, second and third wash - Washing solvent water 50°C

The initial temperature of the refractometer is 21.4°C. In the first wash a total of 40 L of water at 50°C is added to the centrifuge dryer. The temperature at the refractive index changes from 21.4°C to a max value of 30.5°C, as shown in Figure 54.

During the second wash 200 L of water at 50°C is added to the centrifuge dryer. Gradual increase in temperature is shown in the second wash, with a washing solvent at 50 °C. The temperature changes from 26.9 °C at the start of the second wash to 41.83°C at the end of the second wash. Changes in temperature at the RI-meter are slow and take a long time as the flow of washing solvent exiting the cake is high. The resulting heat transfer from the passing washing solvent to the refractometer is poor.

With increasing temperature of the RI a decrease in RI value is observed, as shown in Figure 55. On the left y-axis the refractive index is given in orange. On the right y-axis the temperature is given in red. Both variables are plotted against the time. Point 1 and point 2 are the beginning and end of the first wash. Point 3 and point 4 are the beginning and end of the second wash. Point 5 and 6 are the beginning and end of the third wash.

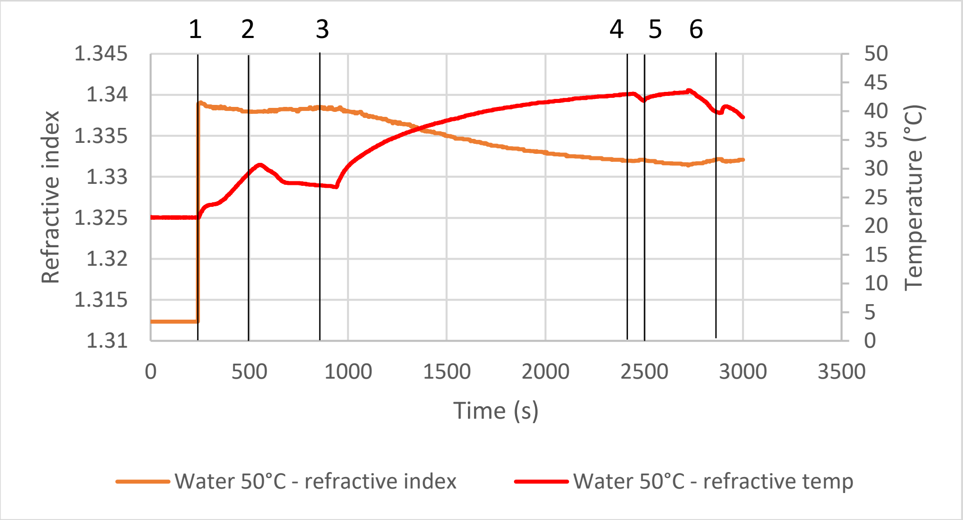

Figure 55 Influence of temperature on the refractive index - Washing solvent water 50°C

All numbers and corresponding temperature and refractive index values are given in Table 30.

Table 30 Refractive index and temperature of numbers in Figure 55

Number in Figure 55	Refractive index	Temperature (°C)
1	1.3387	21.46
2	1.3380	28.82
3	1.3383	26.91
4	1.3320	41.83
5	1.3320	41.84
6	1.3314	43.37

During the first wash a small decrease of the refractive index is detected. The refractive index changes from 1.3387 (**1**) at the beginning of the first wash to 1.3380 (**2**) at the end of the second wash. After the first wash, the temperature keeps rising to a maximum temperature of 30.09°C. Between seconds 517 and 913 no additional washing solvent is added to the centrifuge. The temperature drops to 26.91°C (**3**). The refractive index increases to 1.3380 (**3**) with the decrease in temperature. During the second wash, from 913s to 2480s, the refractive index decreases with increasing temperature. The difference in refractive index between point (3) and (4) is calculated in (4.5):

$$\Delta RI = RI_4 - RI_3 = 1.3320 - 1.3382 = -0.0062 \tag{4.5}$$

The measured temperature effect (K_T) on the refractive index / temperature is calculated below in (4.6):

$$K_T = \frac{\Delta RI}{\Delta T} = \frac{-0.0063}{(|41.83\ °C - 26.91\ °C|)} = \frac{-0.0063}{14.92\ °C} = -0.000423 \tag{4.6}$$

The measured effect of the temperature is -0.000423. This is the change that the refractive index would change if the temperature increased with 1°C. The measured temperature effect, calculated in (4.6), is clearly larger than the temperature effect (-0.0001) in literature. This must be considered when studying the washing curves of the products.

4.2.3. Rotation speed of filtering centrifuge

To test the influence of the rotational speed of the filtering centrifuge on the wash time of a filter cake, a $NaHCO_3$ filter cake of 4 cm was used. 25 kg of $NaHCO_3$ was brought into suspension in 250 L of ethanol as a mother liquor. This suspension slurry was fed to the centrifuge dryer. The filter cake was washed with ethanol and methanol at 500 and 800 RPM. The filter cake was not changed in-between tests as $NaHCO_3$ is non- soluble in ethanol and poorly soluble in methanol (2.13 wt%). The amount of washing solvent used and rotational speed of the centrifuge during the washing process are given in Figure 56. The amount of washing solvent on the left y-axis is shown in blue. The RPM speed of the filtering centrifuge on the right y-axis is given in black. The numbers (1) and (2) show the change in washing solvent from ethanol to methanol. Washing solvent is only added to the centrifuge when the amount of washing solvent increases. During plateaus in the graph no washing solvent is added.

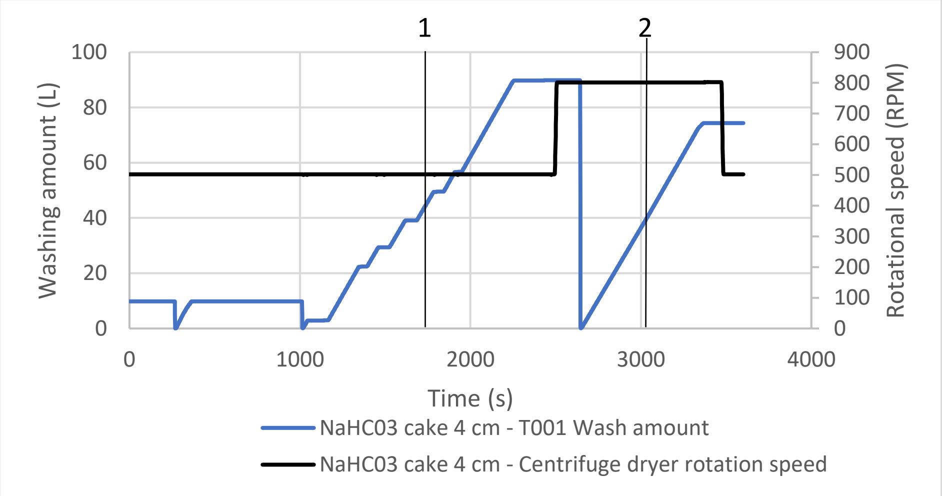

Figure 56 Rotational speed of filtering centrifuge and amount of washing solvent added during tests of the influence of rotational speed on the washing cure –$NaHCO_3$ filter cake 4 cm

The refractive index of the tests is given in Figure 57.

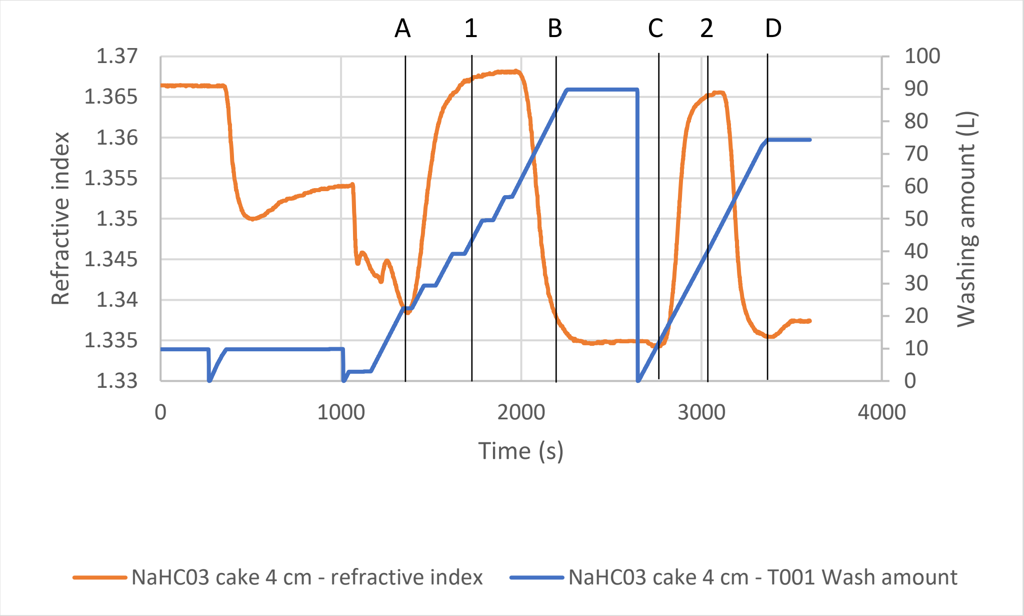

Figure 57 Influence of rotational speed of filtering centrifuge on washing time - Refractive index and amount of washing solvent (L)

First a technical wash with 10 L of ethanol is done. After the technical wash a decrease in refractive index is measured. This is not expected as the filter cake is washed with ethanol, with a refractive index value of 1.362. However, the decrease in refractive index is probably due to the displacement of leftover methanol in the filter cake. The filter cake during this test was re-used from previous tests, where methanol was used as the last washing solvent. Methanol has a refractive index value of 1.329, which would explain the decrease of refractive index. During the first normal wash the refractive index increases towards the refractive index value of pure ethanol. The solvent switch occurs at number 1. The refractive index drops again towards the refractive index of methanol. Between the first and second washing the RPM were changed from 500 RPM to 800 RPM. The increase and decrease in refractive index, as in the first washing, is repeated during the second washing.

The first increase and decrease in the refractive index during the second washing (A-B) clearly takes longer than the during the third wash (C-D). The time of this increase and decrease is calculated below in (4.7) and (4.8).

$$\Delta t_{A-B} = 2351\ s - 1386\ s = \ 965\ s \tag{4.7}$$

$$\Delta t_{C-D} = \ 3383\ s - 2773\ s = 610\ s \tag{4.8}$$

The first wash at 500 RPM clearly takes longer than the second wash at 800 RPM with the same filter cake and same washing solvents. These results conclude that increasing the rotational speed shortens the washing time of a filter cake. However, it should be taken into account that $NaHCO_3$ is a low resistance and low compressible product. High resistance product may not show the same results since the filter cake may be compressible. Increasing the RPM speed when working with highly compressible products would only increase the resistance and thus increase the washing time.

4.3. Washing curves

4.3.1. Alios T3728

Alios T3728 is a product with a hair like crystal structure and a high cake resistance. The washing curve of Alios T3728 batch I18CD0989 is given in Figure 58. The batch consist out of 2 loads, load 1 in blue and load 2 in orange. The refractive index on the left y-axis is given by dotted lines. The amount of washing solvent on the right y-axis is given by solid lines. The product is washed with a Isopropyl Acetate (IPAc) / Heptane mixture with a 1:4 volume ratio.

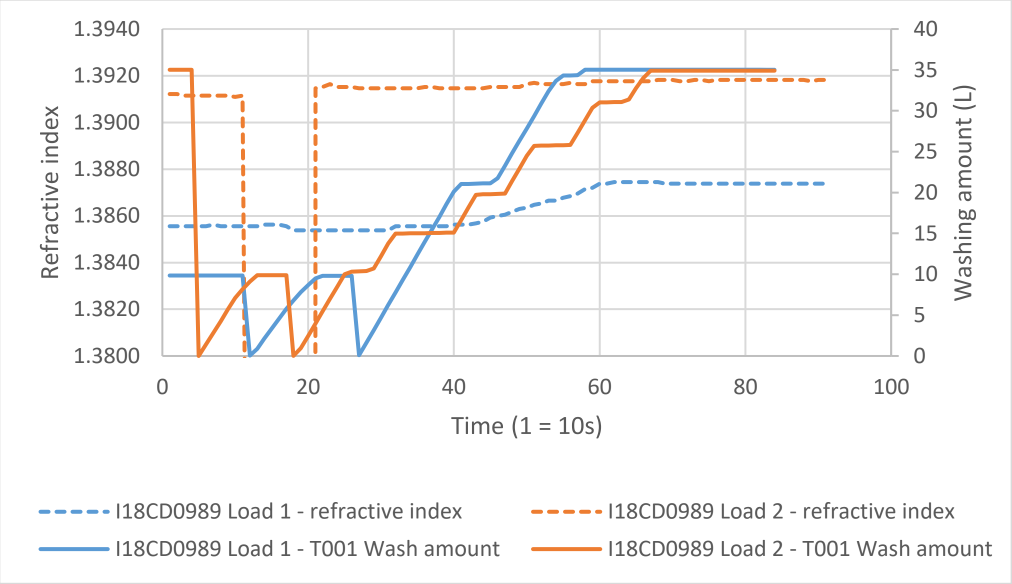

Figure 58 Alios T3728 batch I18CD0989 ideal washing curve

For each load, first a technical wash is done. The technical wash does not show any immediate effect on the refractive index. After the technical wash, the product is washed with 35 L of IPAc/Heptane mixture. Figure 58 clearly shows a big difference between load 1 and load 2. This difference is due to the reactor wash that is done before the washing of load 2. The influence of the reactor washing on the refractive index curve will be further discussed in 4.3.1.1.

The refractive index value before washing is 1.3856. After about 21 L of washing solvent is added to the filter cake, the refractive index starts to change. This is due to the washing solvent breaking through the filter cake. Alios T3728 is a product with a high cake resistance, resulting in long washing times. The refractive index will not change immediately after the start of the washing, but will take a while, as the washing solvent needs to break through the high resistance filter cake. After 21 L of washing solvent is added, the refractive index changes from 1.3856 to 1.3874. The increase of 0.0018 in refractive index takes 240 s. After this increase, the refractive index remains equal, as no additional washing solvent is added. Load 1 from batch I18CD0989 will be considered the golden batch and all other batches will be compared to this. This batch was chosen, because the process parameters remained constant after this batch. The curve had no additional deviations that not could be explained. The curve little drifting of the refractive index and showed a clear increase in refractive index.

The results of the washing curves will be separated by load, since reactor washing has a large effect on the washing curve. For every batch, the last load will be plotted and discussed separately. The washing curves of batches I18BD0752, I18BD0753, I18CD0817, I18CD0821, I18CD0926,

I18CD0927, I18CD0989, I18CD0990, I18CD1087 and I18CD1088 are given in Figure 59 and Figure 60. The dry load weight after washing and drying is also given.

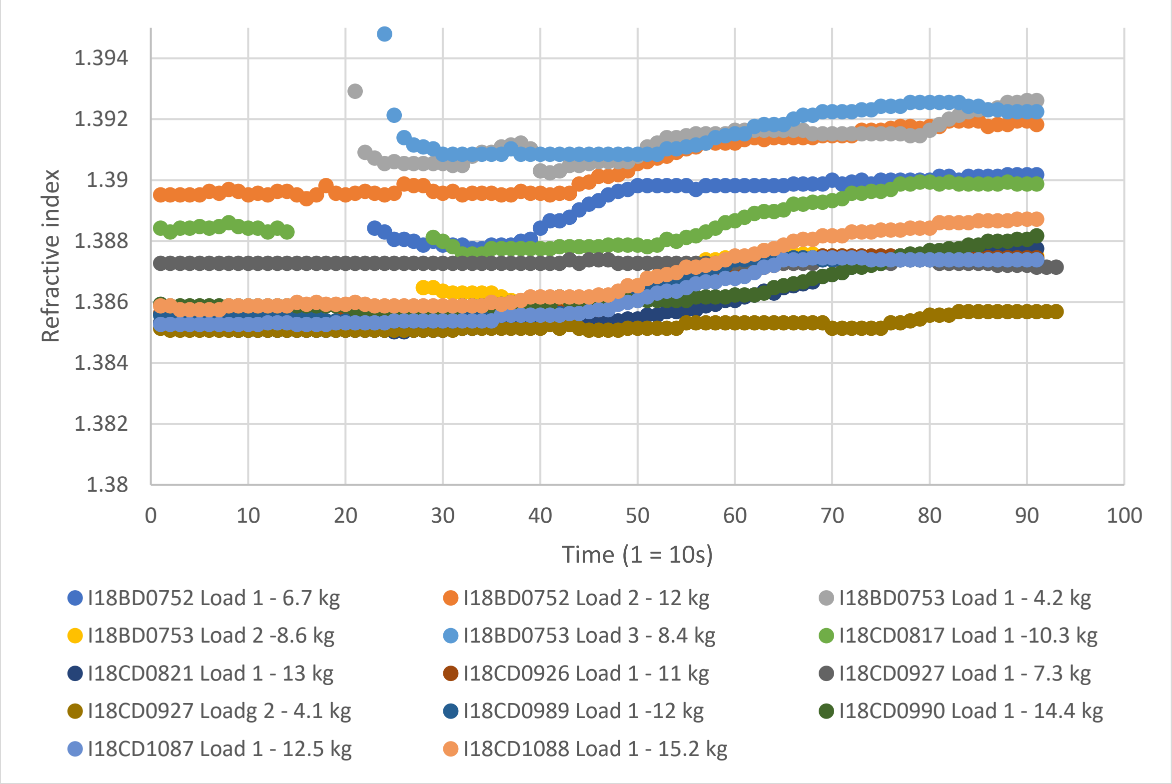

Figure 59 Alios T3728 washing curves - First loads - RI to time

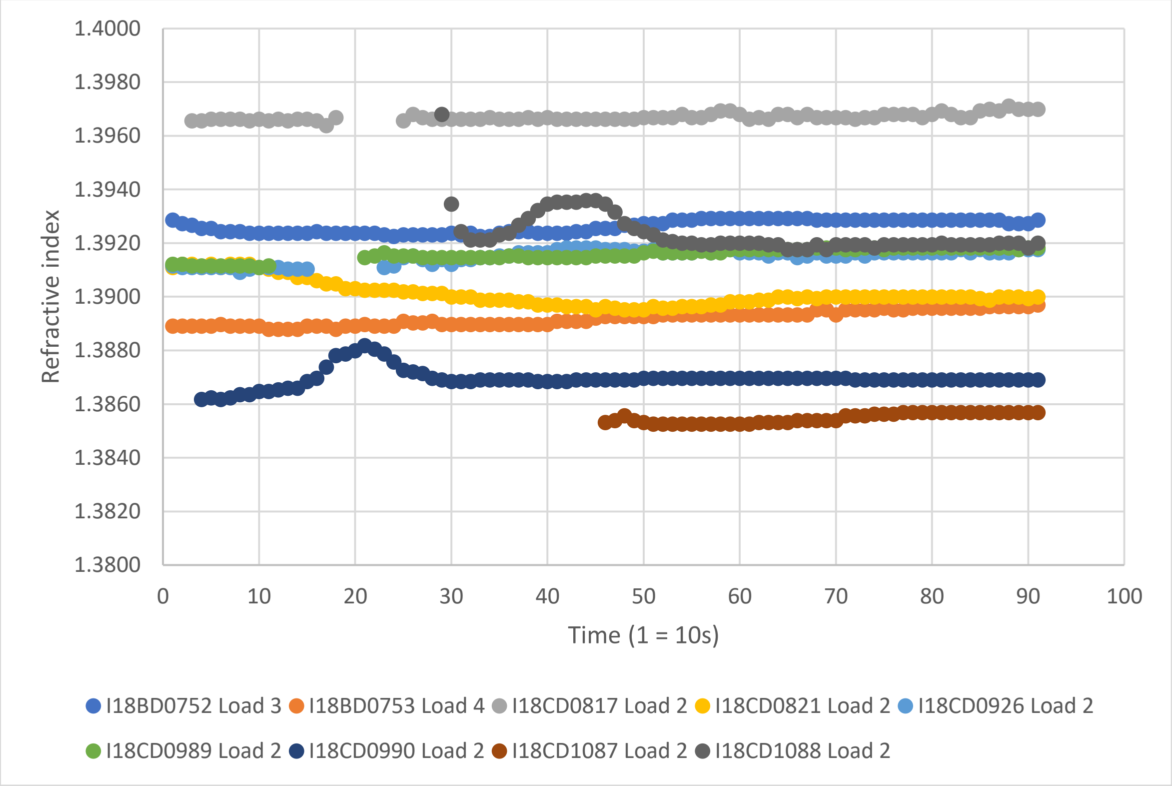

Figure 60 Alios T3728 washing curves - Last load - RI to time

In Figure 59 there is a big difference in the refractive index curves between batches and loads. The trends of the refractive index are generally the same, as an increase of about 0.0018 in refractive index is measured for almost every batch and load. The difference in refractive index because of the reactor washing clearly shown in Figure 59 and Figure 60. The deviations of the curves will be discussed below in 4.3.1.1, 4.3.1.2 and 4.3.1.3.

4.3.1.1. Reactor washing

To discuss the effect of the reactor wash, the washing curves of load 1 and load 2 of batch I18CD0989 are compared. The results are shown in Figure 61. The left y-axis shows the refractive index. The refractive index of load 1 is given in a blue dotted line and the refractive index values of load 2 are given in a red yellow dotted line. The amount of washing solvent is shown in blue and yellow solid lines for load 1 and load 2. During the reactor wash, an amount of 40 L of IPAc/Heptane (1:4 vol) was used to clean the reactor from residual slurry. This extra amount of washing solvent is displayed in Figure 61 as the sudden increase in amount of washing at 40 s. Each time a washing commences the refractive index resets. For example, at 650s the technical wash commences.

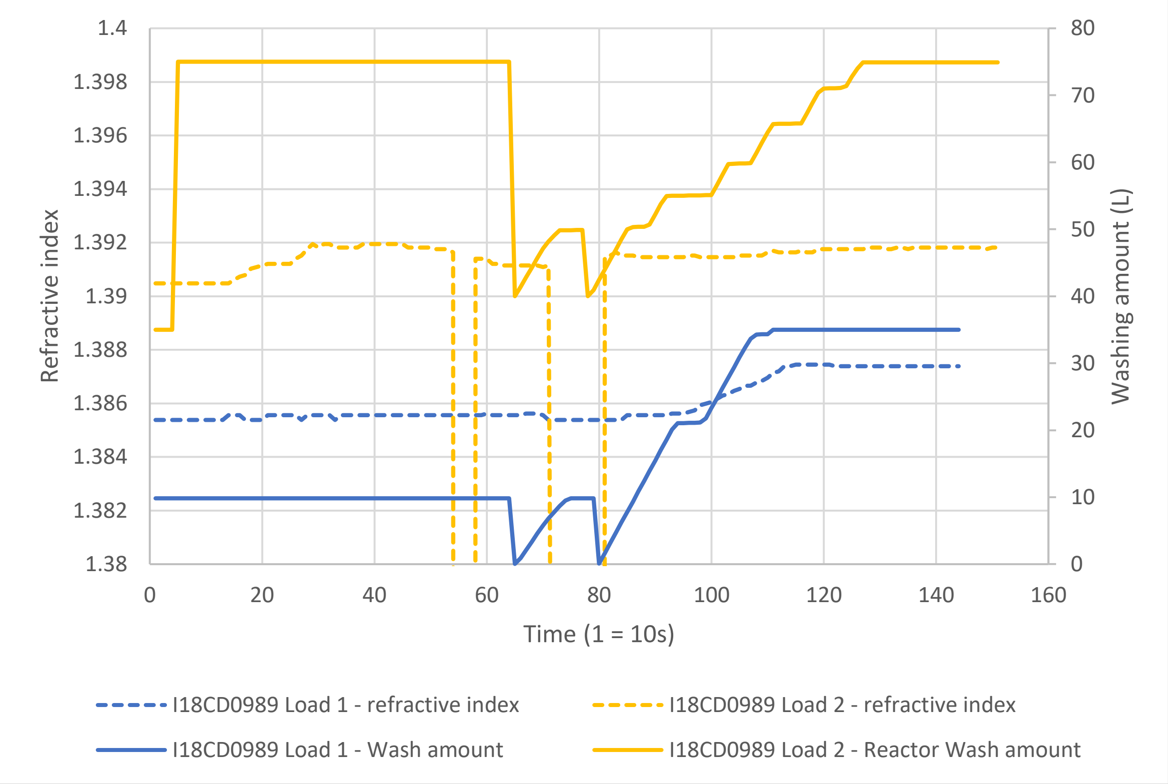

Figure 61 Washing curve batch I18CD0989 - reactor washing effect

As discussed before in 4.3.1 and shown in Figure 60, the last load of every batch does not show any change in the refractive index during the washing process. The change in refractive index of 0.0018 that was measured for the first loads of the batch occurs before the washing commences. As shown in Figure 61, the refractive index of load 2 changes before washing commences. The refractive index changes from 1.3905 to 1.3919. This change is measured during the reactor wash. The amount of washing solvent of the reactor wash (40 L) is about equal to the amount of washing solvent used for a normal wash (35 L). The refractive indicates that the reactor wash has the same effect than the normal washing. Concluding that no additional normal wash should be done when a reactor wash is done. This must be checked using sample tests, as specific impurities could still be too high after the reactor washing. Increasing the amount of washing solvent that is used during the reactor wash could also be an option to reduce the concentration of impurities in the filter cake.

4.3.1.2. High filling weight

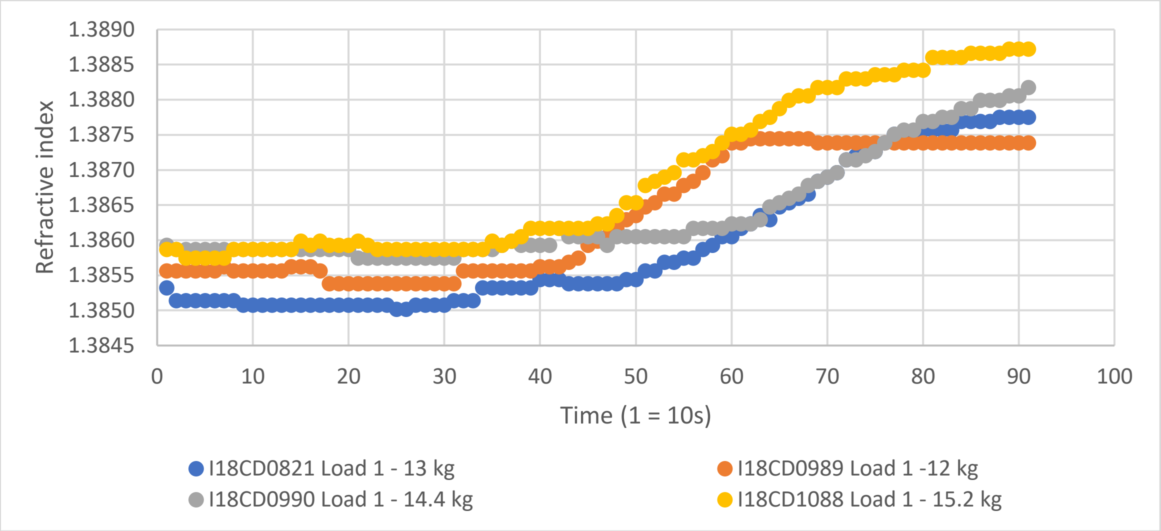

Figure 62 Influence of filling weight on washing curve - Refractive index to time

The filling weight of the centrifuge dryer does influence the washing curves, as shown in Figure 62. Higher filling weight increase the amount of product in the centrifuge dryer. A higher amount of product can be linked to an increased cake resistance. This increased cake resistance decreases the flow of washing solvent through the filter cake. 'Stretching' of the washing curve occurs at batches and loads with a filling weight equal or above 13 kg. Stretching of the washing curve is the increase of washing time. The changes in refractive index and time spent washing for batches I18D0821, I18CD0989, I18CD0990 and I18CD1088 are summarised in Table 31.

Table 31 Influence of filling weight on washing curve - Change in RI and time spend washing – batches I18D0821, I18CD0989, I18CD0990 and I18CD1088

Batch/ Load	Change in RI	Time spent washing (s)
I18CD0821 Load 1	0.0028	570
I18CD0989 Load 1	0.0018	240
I18CD0990 Load 1	0.0022	360
I18CD1088 Load 1	0.0023	430

The changes in refractive index and time spent washing for the batches at higher weight loads are on average larger. Load size should be kept under 13 kg to avoid increased washing times and increased refractive index changes.

4.3.1.3. Crystal morphology

Particle size and particle shape have a big influence on the filtration and washing of a liquid/solid system. Solid particles are rarely either spherical or uniform [34]. Which makes it hard to create a uniform model for the influence of the particles on the filtration or washing of the filter cake.

Batch I18CD0927 of Alios T3728 had a deviation in crystal morphology. The washing curves of batch load 1, load 2 and load 3 are given in Figure 63.

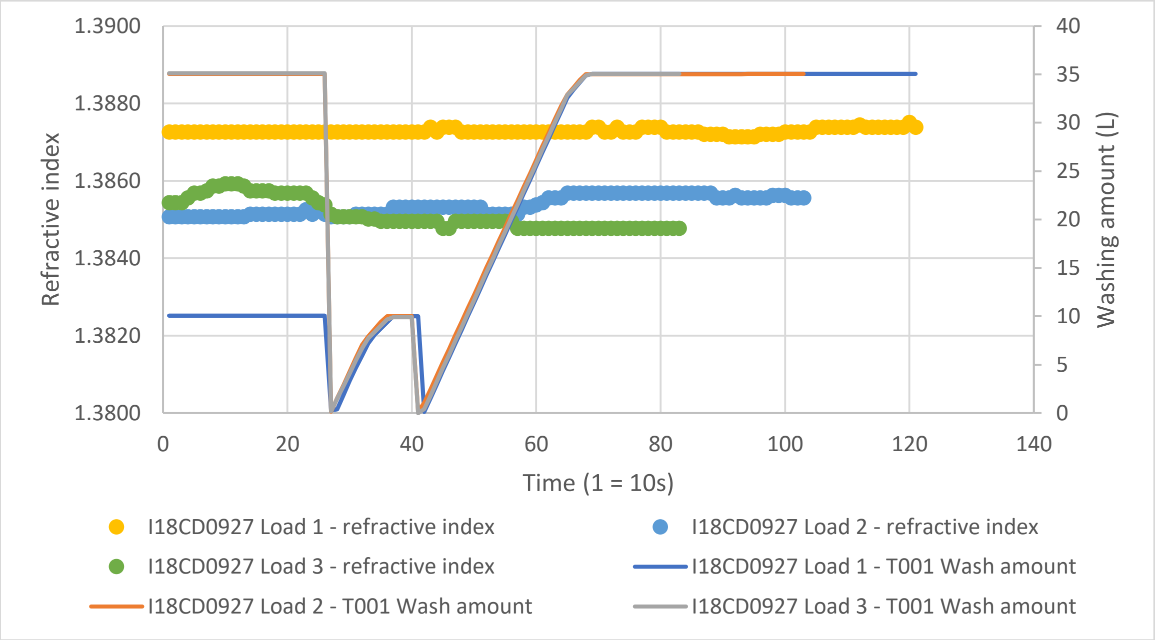

Figure 63 Influence of crystal morphology - washing curve of batch I18CD0927

The change of 0.0018 in the refractive index during the washing is not detected in this batch. The maximum change in refractive index that was measured during the washing was 0.0005. The refractive index shows almost flatlining during the washing process. This is due the change in crystal morphology. The crystal morphology has a clear impact on the washing and filtration process. The washing curve, measured by the refractometer, show a clear difference with the golden batch curve in Figure 58. Using the refractive index, deviations in crystal morphology compared to the golden batch can be detected. Although washing curves of batches with good crystal morphology have to be known to compare.

4.3.1.4. Deviations

Although the refractive index washing curve show the same trend in Figure 59, there is still a large difference between the batches. The start and end refractive index values have large differences. The process parameters that were studied are the following:

- Way of washing
- Filling weight
- Washing solvent / kg

The influence of the way of washing was studied. Certain batches were washed in a stepped way, other batches were washed stepless. The difference between step washing and stepless washing is discussed in 3.3.1.2. The difference in washing did not influence the washing curves in any direct way.

The filling weight of each load and batch varied heavily. At the start, only small batches of 7-8 kg dry weight were filtrated and washed. This was due the D classification of Alios T3728. This classification recommends filtrating with low filling weights and low RPM to prevent a filter cake with a high resistance. The filling weights were increased towards dry weights of 12-13 kg at a later stage. Because of optimisation of this parameters, there is a large change in filling weight between the batches and loads. The filling weight influences the washing curves and their effect. The effect of large fillings is discussed in 4.3.1.2. No other correlation between the filling weight of each load and the refractive index has been found. Further research should be done to determine the correlation between the filling weight of the centrifuge dryer and the refractive index washing curves.

The amount of washing solvent per kg dry product stayed constant for each batch and load throughout production.

No explanation for the large difference between begging and end refractive index could be found. Sampling before, during and after the washing could help finding an explanation. Additional process parameters of the crystallisation should also be taken into account when studying the washing process of this product. Changes such as morphology, as batch I18CD0927, influence the refractive index washing curves greatly.

4.3.1.5. Good washing curves

Figure 64 shows selected refractive index washing curves. The criteria of the selected batches are the following. Only batches upward of batch I18CD0926 are selected, as the process parameters remained constant. Batches with filling weights above 13 are excluded, since filling weights above 13 kg show larger deviations to the golden batch as discussed in 4.3.1.2. Due to different crystal morphology, batch I18CD0927 is also excluded. The resulting selected batches I18CD0926 (grey), I18CD0989 (green) and I18CD1087 (brown) are shown in Figure 64. The dry load weight after washing and drying is also given.

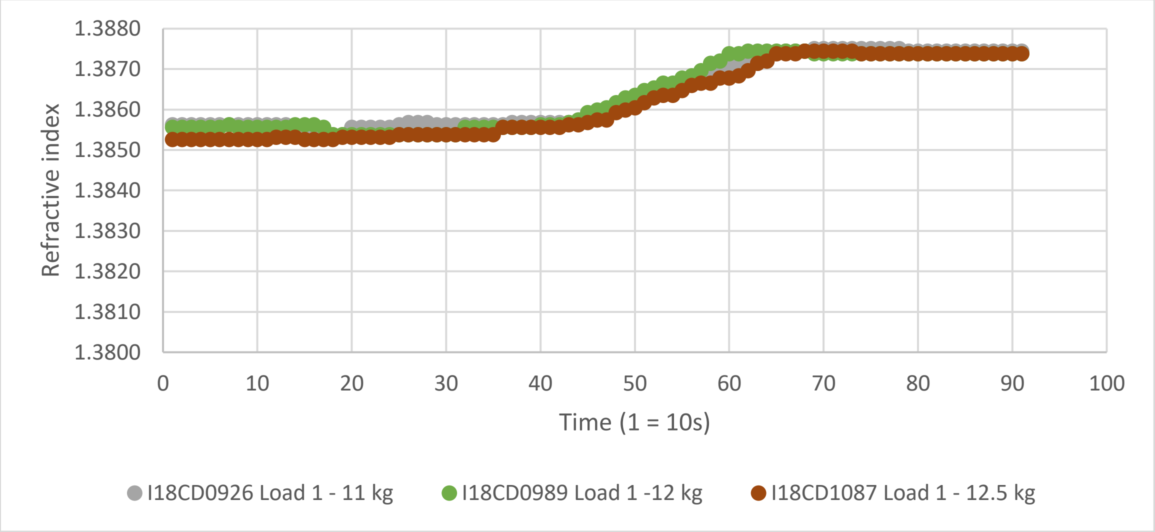

Figure 64 Selected washing curves of Alios T3728 excluded large deviations and high or low filling weights

The refractive index of the washing curve with equal filling weights, process parameters and no large deviations are the same. From the golden batch I18CD0989 a theoretical curve is plotted. Batch I18CD0926 and batch I18CD1087 are compared to this theoretical curve. The theoretical curve is given in black in Figure 65.

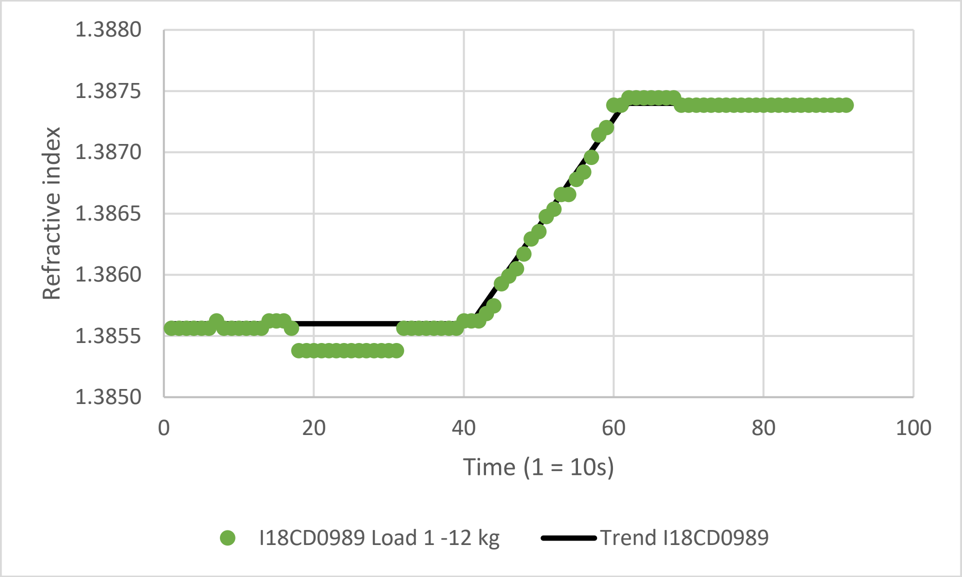

Figure 65 Theoretical trend curve of golden batch I18CD0989

Of the golden batch I18CD0989 a theoretical linear curve was calculated. The theoretical curve consists out of 3 parts: a flatline, a linear increase and another flatline. The first flatline is equal to a refractive index value of 1.3856. The linear increase follows the function RI= 0.000088*time+1.3856.

The flatline after the increase is equal to a refractive index value of 1.3874. The correlation between measured values and theoretical calculated values of the trend is given in Table 32.

Table 32 Correlation of batch I18CD0926, I18CD0989 and I18CD1087 to the theoretical calculated curve of batch I18CD0989

Batch	Correlation to theoretical curve
I18CD0926	0.9892
I18CD0989	0.9969
I18CD1087	0.9888

The correlation is high between the batches and the theoretical trend curve. This could be used for future batches, if the criteria are followed.

4.3.1.6. Summary of effects and deviations Alios T3728

The deviations and effects on the refractive index washing curves are summarised in Table 33.

Table 33 Summary of effects and deviations in washing curves of Alios T3728

Effect or deviation	**Alios T3728 washing**
Effect of technical washing	No
Refractive index change during washing	+ 0.0018
Equal start point	No (after selection yes)
Equal end point	No (after selection yes)
Trend of curve	Flatline, linear trend, flatline
Reactor washing effect	Yes
Effect of high filling weight	Stretching of washing curve
Effect of different crystal morphology	Flatline of refractive index during washing

4.3.2. Alios T3730

The washing curve of Batch I18DD1274 is given in Figure 66. The added amount of washing solvent is given in blue, the refractive index values are given in orange. Both variables are plotted on a time scale.

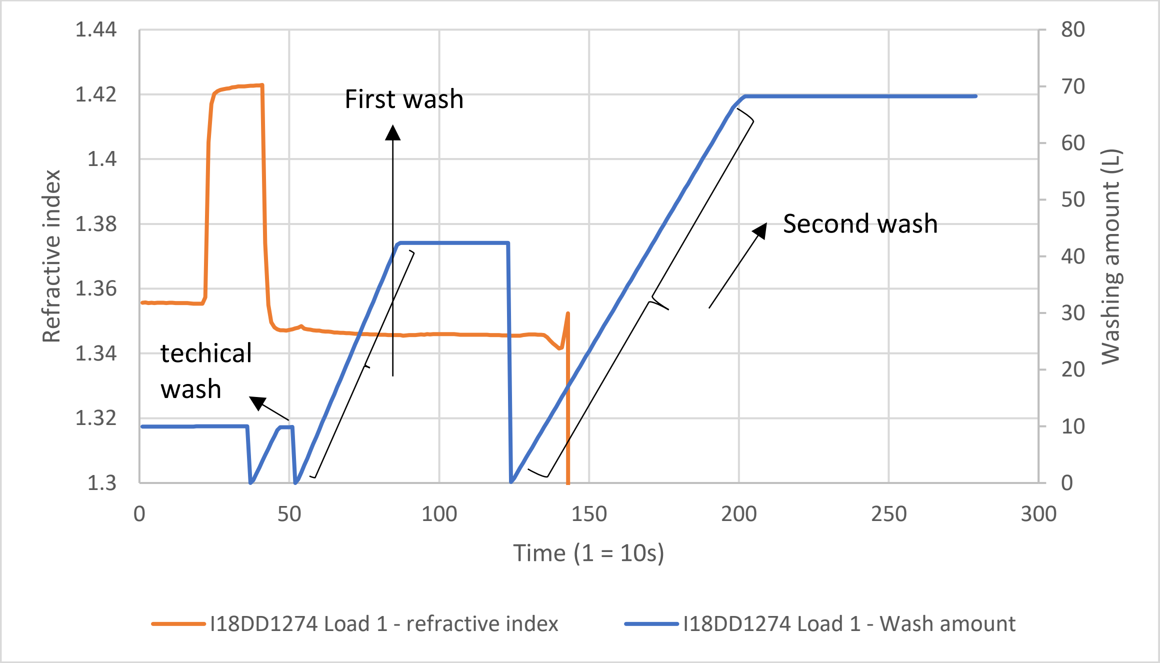

Figure 66 Alios T3730 batch I18DD1274 ideal washing curve

The refractive index shows big changes during the washing process. These changes in refractive index will be discussed in detail for batch I18DD1274. Other batches will be compared with this batch. First a technical wash with 10 L of Acetonitrile/Water through the washing lance is done.

During the first wash, after the technical wash, the filter cake is washed with a total of 42.4 L Acetonitrile/Water (1:2.5 vol) mixture. Lastly the filter cake is washed with a total of 68.3 L pure water during the second wash.

To discuss the refractive index in detail, the changes are indicated with numbers in Figure 67.

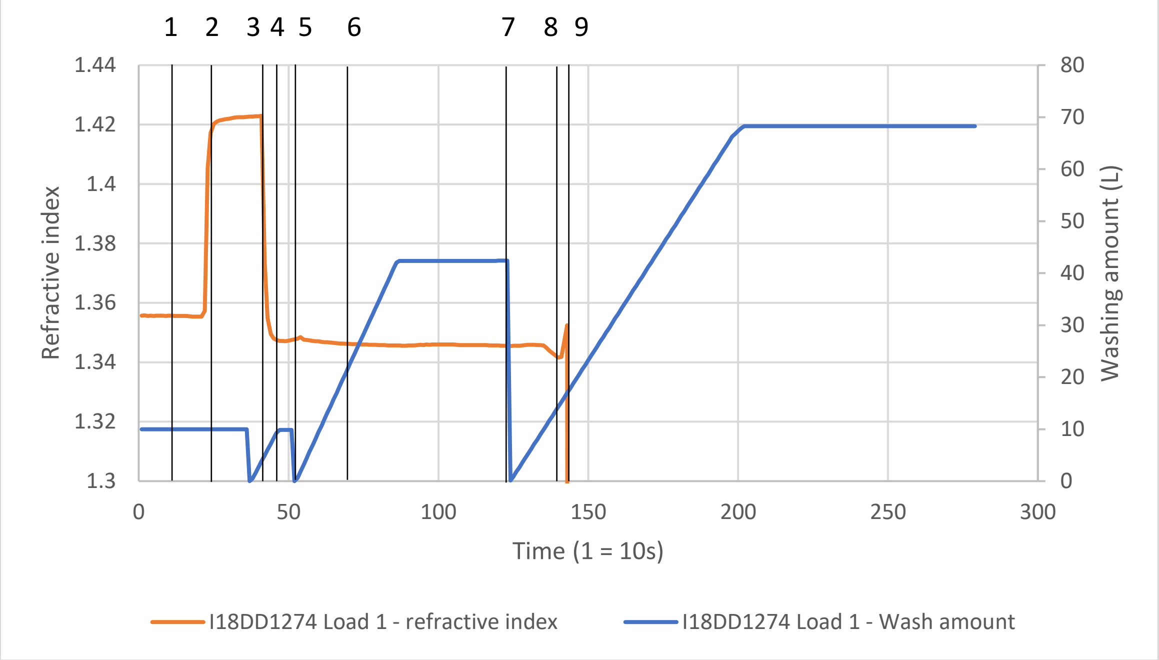

Figure 67 Alios T3730 batch I18DD1274 ideal washing curve - numbered

The different changes in refractive index are marked with numbers (**1-2-3-4-5-6-7-8-9**). In Table 34 an overview of the different numbers and their corresponding RI value is given.

Table 34 Refractive index values of numbered items in Figure 67

Marked number in Figure 67	RI value
1	1.3553
2	1.4202
3	1.4230
4	1.3472
5	1.3487
6	1.3467
7	1.3456
8	1.3410
9	1.3568

The refractive index starts at a value of 1.3553 (**1**) before the washing procedure. A big increase of refractive index is detected before the washing step commences. The refractive index spikes from 1.3553 (**1**) to 1.4202 (**2**). After the initial spike, the RI keeps slowly increasing from 1.4202 (**2**) to 1.4230 (**3**). This large change in refractive index could not be explained. Since the increase happens before the washing process, it is possible that this is a product in the mother liquor. The product in the mother liquor could cause an increase in refractive index before the washing commences as it exits the cake after the filling of the centrifuge dryer. A significant increase in concentration of the mother liquor could cause a big increase in RI. When the 4 L is added during the technical wash, the RI drops from 1.4230 (**3**) to 1.3472 (**4**). This drop in RI is due to the technical washing solvent (Acetonitrile/Water (1:2.5 vol)) that passes through the filter cake and eventually measured by the refractometer PR-23. During the technical wash, the value of 1.3472 is maintained. After the technical wash, the first wash commences. A spike to 1.3487 in RI value is measured after the addition of 1.6 L of the first washing solvent (Acetonitrile/Water (1:2.5 vol)). This spike is due to the displacement of impurities. The change in concentration in the washing solvent causes a small increase in RI. After the initial spike, the RI decreases slowly to a value of 1.3467 (**6**). Further decrease of the RI is measured from 1.3467 (**6**) to 1.3456 (**7**), at the end of the first wash. This decrease in RI is due to the temperature effect. The effect of the temperature is calculated below in (4.9):

$$(\mathbf{6}-\mathbf{7}): \Delta T = \mid 14.0\ °C - 17.5\ °C \mid = 2.5\ °C = -0.00025 \tag{4.9}$$

The RI decreases from 1.3467 (**6**) to 1.3456 (**7**). This is a difference of 0.0011, which could be dedicated to the temperature effect. Besides the temperature effect, the solvent ratio will also affect the RI. The effect of the Acetonitrile/Water ratio on the RI is 0.0023 %, as given in Table 26. The absolute error is calculated in (4.10):

$$RI\ Error_{solvent\ ratio} = \frac{0.023}{100} * 1.3467 = 0.00031 \tag{4.10}$$

Together with the temperature effect this explains 0.0005 of the 0.0011 in RI difference between (**6**) and (**7**). The other 0.0006 difference in RI could also be due to temperature effect. In 4.2.2 the temperature effect in the centrifuge dryer setup was larger than the temperature effect of the literature. During the second wash, after the addition of 14.8 L of water, the RI decreases from 1.3458 to 1.3410 (**8**). The drop in RI is due to the second washing solvent, pure water, that passes through the filter cake. The RI value of pure water is 1.333, which is lower than the 1.3456 RI value during the first wash. Washing with a solvent with a lower RI value causes the value to decrease as the ratio of water becomes bigger. After the drop, the RI increases again to a value of 1.3568 (**9**). This increase is due to the displacement of the first washing solvent and the removal of impurities in the filter cake. After the max value of 1.3568 is reached, the RI drops to 0. At this time, no liquid passes over the refractometer and the refractive index of air is measured. Since the refractometer only measures the RI of liquid, the value drops to 0.

The washing trends of the batches I18DD1274, I18DD1340 and I18DD1367 are plotted by load. Alios T3730 is a product with a crystal structure that is an unstable polymorph. The product has to be filtrated within 24h. Otherwise, the product will change into another polymorph stage. Only the first polymorph is considered the product and any conversion to the other is loss in yield. Because of this property of the product, the loads of each batch are compared. Each load from each batch should be filtrated within the same time frame. For example, is load 2 from batch I18DD1274 is filtrated after 2h, load 2 from batch I18DD1340 will also be filtrated after 2h.

The washing trends of batches I18DD1274, I18DD1340 and I18DD1367 are plotted in Figure 68.

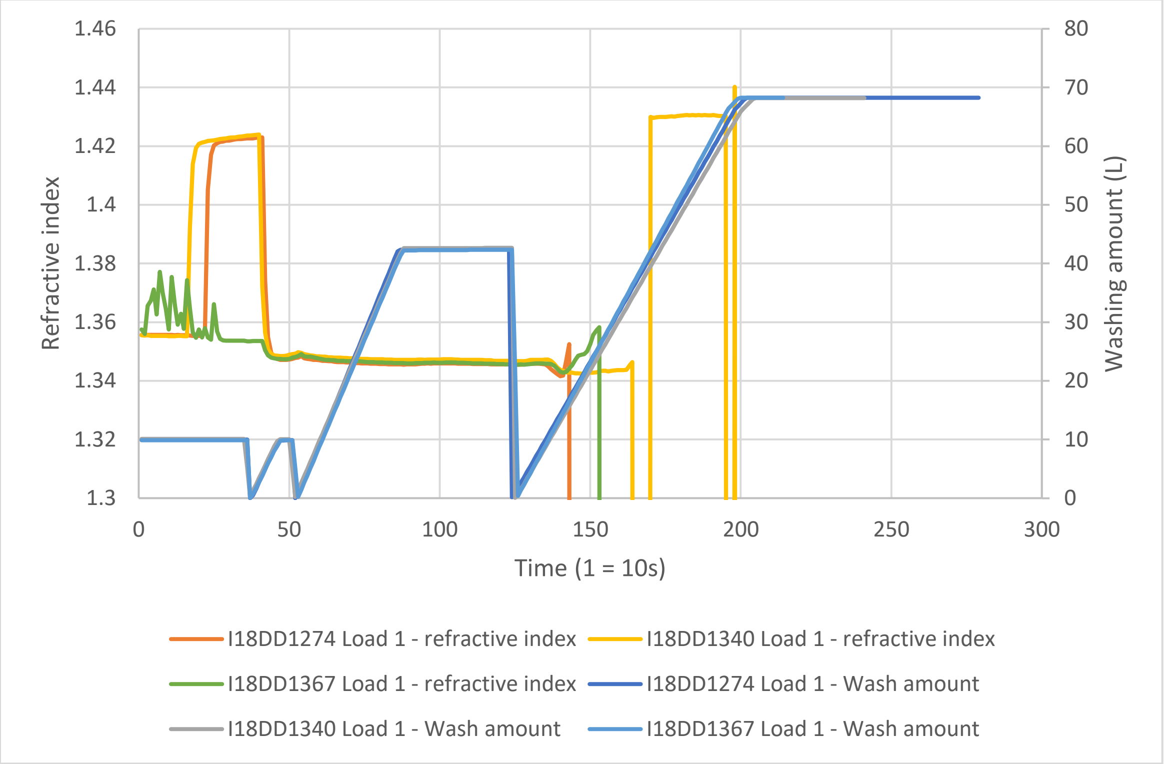

Figure 68 Alios T3730 washing trends batch I18DD1274 load 1, I18DD1340 load 1 and I18DD1367 load 1

Compared to batch I18DD1274, batch I18DD1367 shows spikes before the washing commences. No plateau is reached as in batch I18DD1274 and I18DD1367. No explanation could be found for the difference in batches. Sampling could determine which impurities are measured before the washing commences. This could be linked with the refractive index to explain such deviations.

At the end of the washing curve of batch I18DD1340, the refractive index increases. A plateau is reached at 1.4301. The refractive index remains constant for 220s. This plateau has a similar refractive index as the plateau formed before the washing commences, which is 1.4240. This would imply that in both cases the same product or solvent is displaced from the filter cake. Since the second wash is done with water, which has a refractive index of 1.333. The refractive index of the plateau before the technical wash and during the second wash is much larger. This could be due to a displacement of a certain product during these moments. Sampling during the washing could determine this product that causes the increase in refractive index.

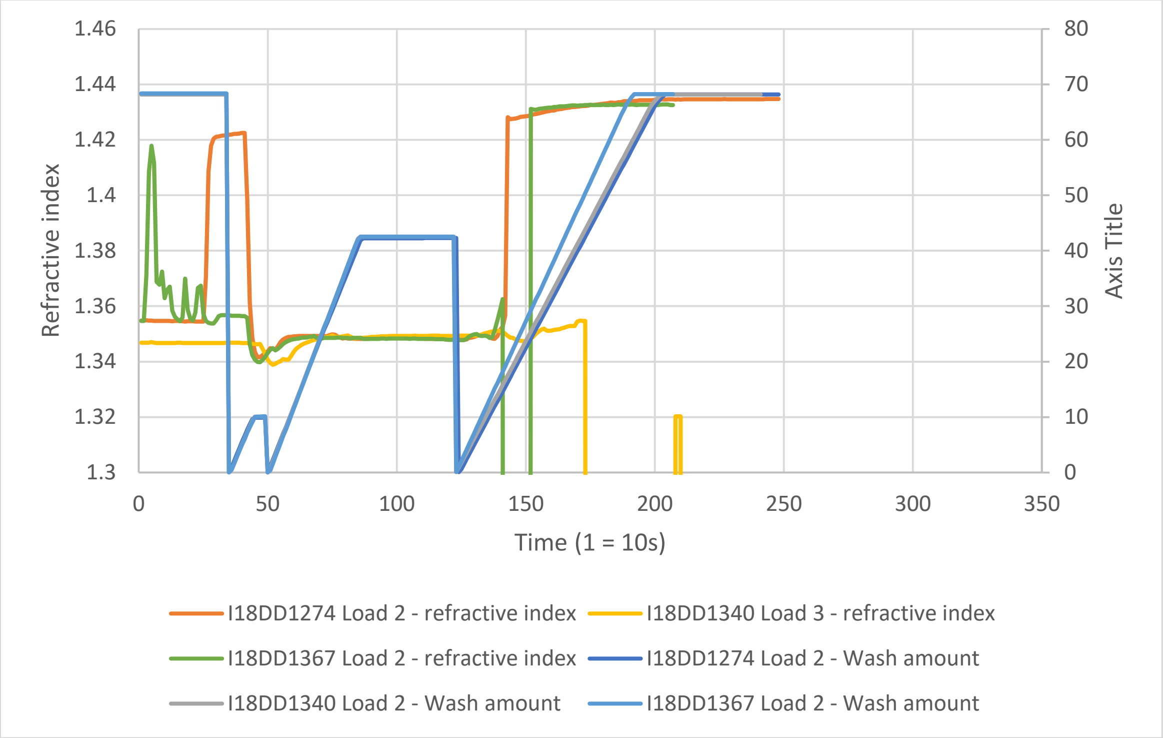

Figure 69 Alios T3730 washing trends batch I18DD1274 load 2, I18DD1340 load 2 and I18DD1367 load 2

The refractive index before and during washing shows the same pattern as in Figure 68. For batch I18DD1274 a plateau before washing and during the second wash was measured. For batch I18DD1367 spikes before the technical wash was again measured.

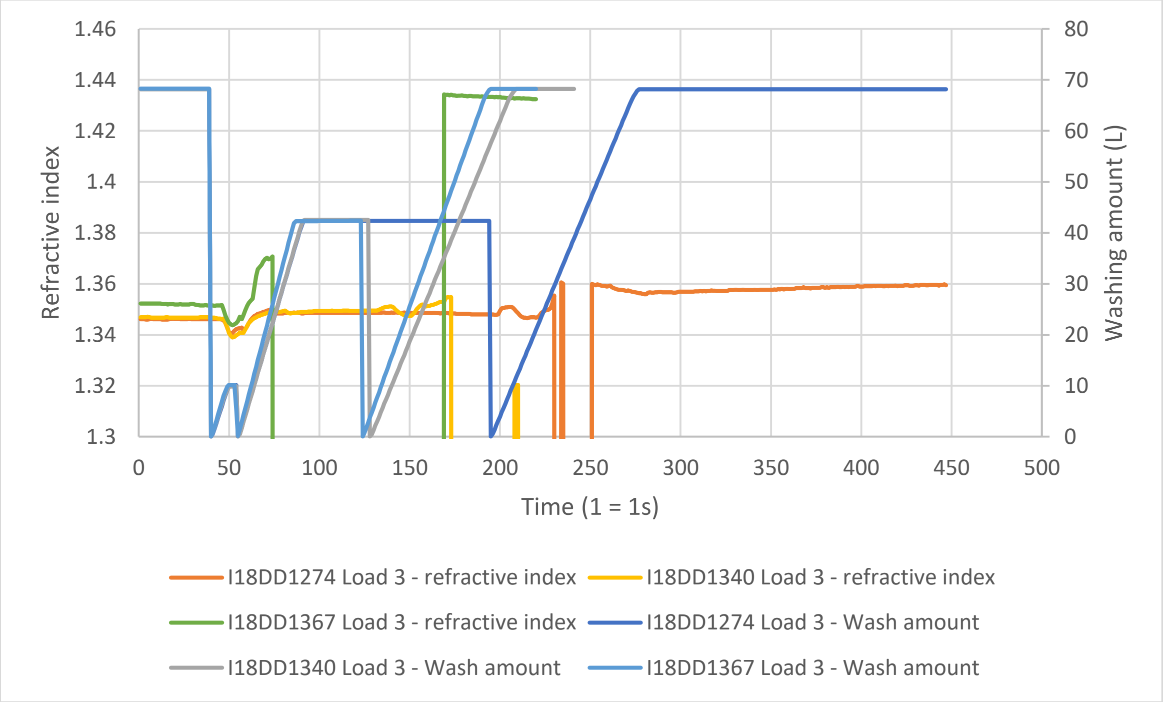

Figure 70 Alios T3730 washing trends batch I18DD1274 load 3, I18DD1340 load 3 and I18DD1367 load 3

Last loads again show large differences with previous batches. This is again to the reactor wash that is done before the technical wash.

4.3.2.1. Summary of effects and deviations Alios T3730

The deviations and effects on the refractive index washing curves are summarised in Table 35.

Table 35 Summary of deviations and effect in washing curves of Alios T3730

Effect or deviation	Alios T3730 washing
Technical washing effect	Yes
Reactor washing effect	Yes
Crystal morphology effect	Different refractive index washing curves between load 1, load 2 and load 3

4.3.3. Alios Crude

The washing curves measured by the refractometer of product Alios Crude will be discussed in this paragraph. First each change in refractive index of batch I18ED1491 will be discussed and explained if possible. Other batches of the product will be compared to this batch, since this batch showed the least deviations in the washing curve. All process parameters, except the filling weight, were constant for all discussed batches.

The washing curve of batch I18ED1491 is given in Figure 71. The added amount of washing solvent is given in blue, and measured refractive index is given in orange. Both variables are plotted on a time scale.

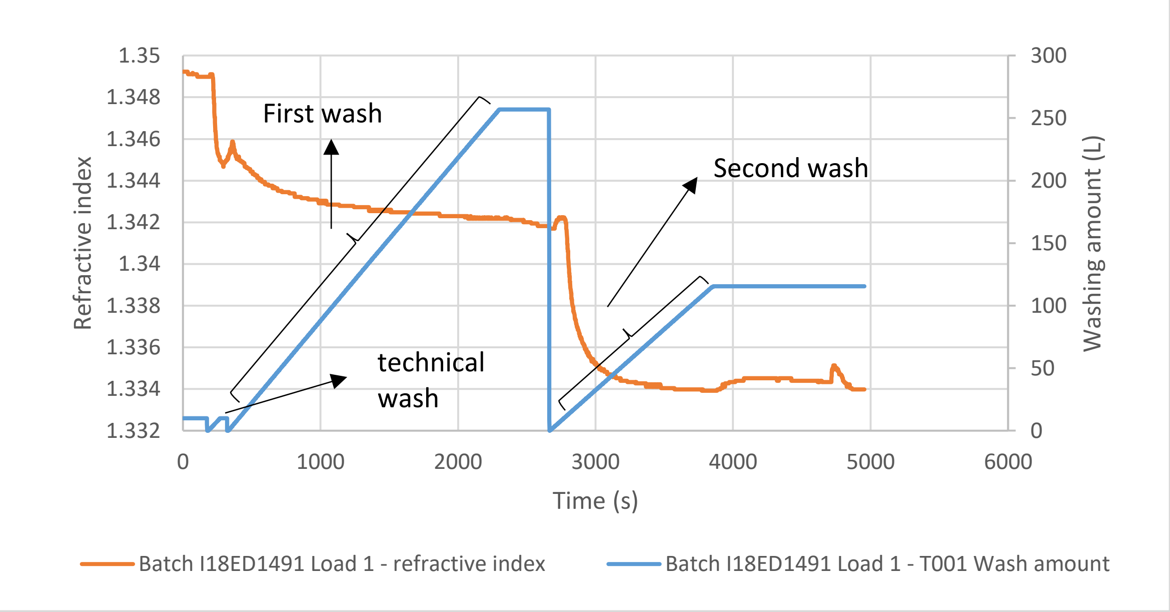

Figure 71 Alios Crude batch I18ED1491 ideal washing curve

As seen in the graph, the refractive index changes heavily during the washing process. First a technical wash with 10 L of Acetonitrile/water through the washing lance is done. After the technical wash the first washing solvent a total of 256.8 L of Acetonitrile/water is added to the filter cake. Lastly the filter cake is washed with 115.6 L of water.

To discuss each change in refractive index, the changes are indicated with numbers as shown in Figure 72.

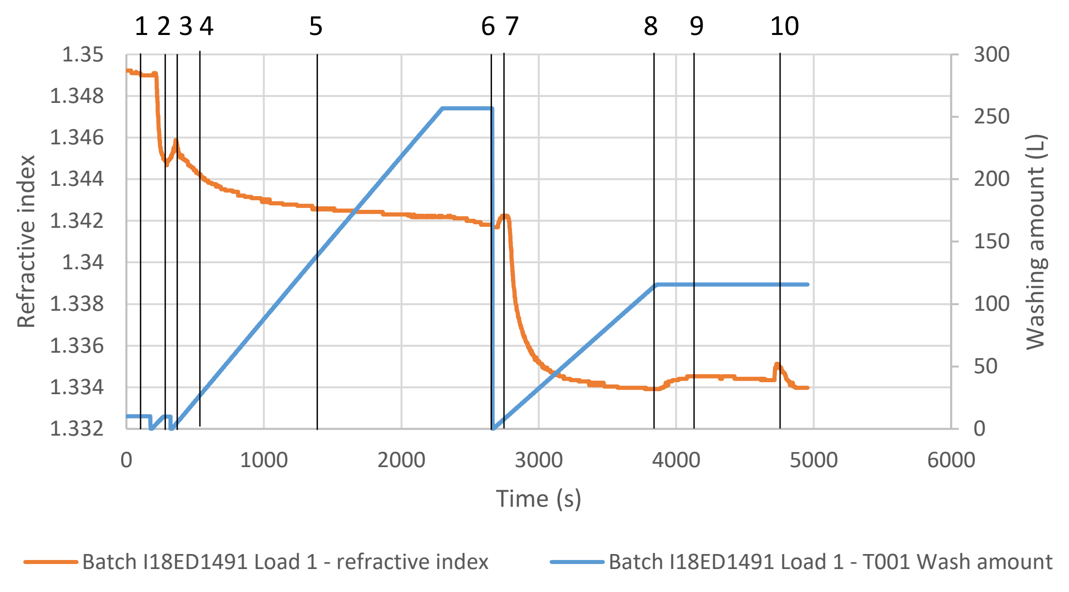

Figure 72 Alios Crude batch I18ED1491 ideal washing curve - numbered

The different changes in RI are marked with numbers (**1-2-3-4-5-6-7-8-9-10**). In Table 36 an overview of the different RI at the marked numbers is given.

Table 36 Refractive index values of numbers in Figure 72

Marked number in Figure 72	RI value
1	1.3490
2	1.3447
3	1.3459
4	1.3447
5	1.3425
6	1.3418
7	1.3422
8	1.3339
9	1.3345
10	1.3351

The first drop in RI is due to the technical washing (10 L) with the first washing solvent. The RI value drops from 1.3490 (**1**) to 1.3447 (**2**) during the technical wash. This drop in refractive index is due to the addition of the 10 L of technical washing solvent. A small amount of washing solvent penetrates through the filter cake and cause a decrease in refractive index. When all 10 L of washing solvent of the technical wash is added, the plateau of the technical wash is reached. The plateau is when no washing solvent is added to the centrifuge and the amount of washing solvent is constant. During this plateau, the RI value increases from the minimum of 1.3447 (**2**) to 1.3450.

An increase in RI is measured during the plateau of the technical wash and the first liters of the first washing solvent. A spike in RI value from 1.3447 to 1.3459 is measured (**2-3**). The maximum value is reached after 4.6 L of the first washing solvent is added. This increase in RI is caused by the displacement of the mother liquor with a high concentration in impurities.

After the maximum value of 1.3459 is reached the RI starts to decrease again. The value of the minimum during the technical washing, 1.3447 (**4**), is reached with the first solvent after addition of 15.4 L. The RI keeps decreasing at the same speed until a value of 1.3425 (**5**) is reached at 135 L.

Further decrease of RI value is measured during the addition of the first washing solvent (**5-6**). This decrease in RI is due to the increasing temperature. The increase of the temperature by 1°C causes an average decrease of 0.0001 in RI. The corresponding RI value is calculated below in (4.11):

$$(\mathbf{5}-\mathbf{6}): 21.2°C - 19.2°C = 2\ °C = -0.0002 \tag{4.11}$$

The RI decreases from 1.3425 (**5**) to 1.3418 (**6**). This is a difference of 0.0007, which could be dedicated to the temperature effect. Though the difference from (**5-6**) is bigger, the difference in RI value could still be due to increase in temperature and change in solvent ratio.

The second washing solvent causes a small spike in RI at the start. This spike in RI is due to the displacement of the first solvent by the second solvent, as a RI value of 1.3422 is reached (**7**). After the addition of 10 L of the second washing solvent, the RI value drops significantly from 1.3422 to 1.3339 (**8**). This drop in RI is during the addition of the total volume (115.6) of second washing solvent (**7-8**).

After the addition of the total amount of washing liquor of the second solvent, a small increase in RI is detected. The RI value increases from a value of 1.3339 (**8**) to a RI value of 1.3345 (**9**). This could be retained second washing solvent that is coming of the cake at a later time. Further testing of this increase in RI value should be done. Lastly a spike in RI is detected 15 min after the end of washing with washing solvent 2. This spike in RI is due to the pressurized advanced centrifugation (PAC), where any remaining liquid in the filter cake is forced out of the cake. The liquid is forced out of the cake using a N_2 flow of 1000 Nm^3/h.

The washing trend of batches I18DD1429, I18ED1491, I18ED1558, I18ED1571 and I18ED1572 are given in Figure 73. The refractive index of the batches during the washing is given on the left y-axis. The amount of washing solvent that has been added to the cake is given on the right y-axis. The amount of washing solvent resets to zero each time a washing step is done. Also, the refractive index values of the pure washing solvents are drawn on the chart.

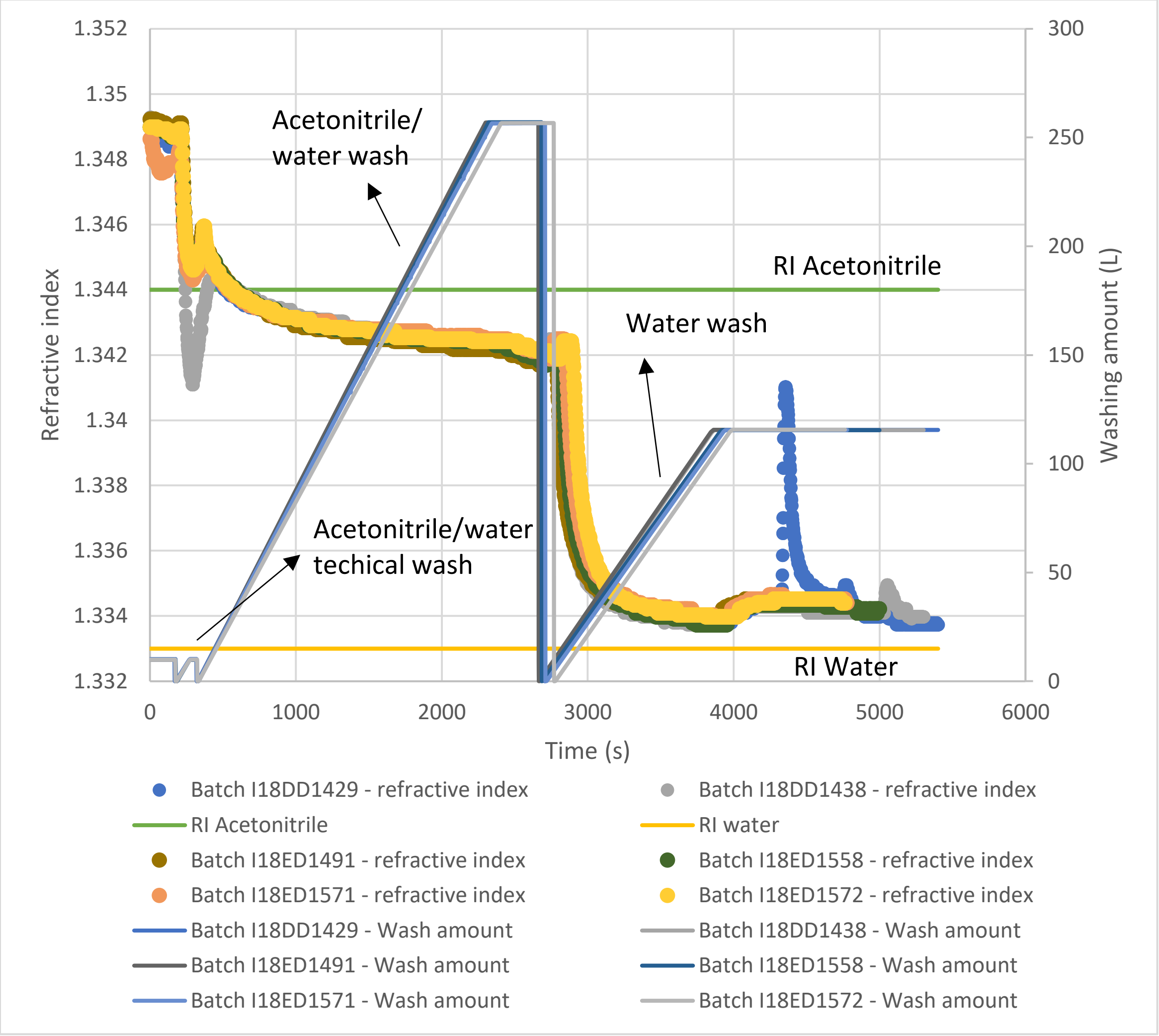

Figure 73 Alios Crude washing trends of batch I181429, I18DD1438, I18ED1491, I18ED1558, I18ED1571, I18ED1572

4.3.3.1. Deviations

This paragraph will discuss the big deviations in washing trend between the washing curves given in Figure 73. The washing trends will be compared to batch I18ED1491, which has been thoroughly discussed in 4.3.3. This batch was selected as 'golden batch' as it showed no deviations that were unexplainable. Apart from the filling weight, all batches have the same process parameters.

Batch I18DD1438 shows a deviation to the 'golden batch' washing curve at the beginning of the technical wash. A drop in refractive index from 1.3486 to 1.3410 is measured. The golden batch also shows a drop in refractive index, but only to 1.3447. This difference of 0.0037 could be explained by demixing of the washing solvent mixture. During the drop, the refractometer measures the breakthrough from the washing solvent through the cake, as discussed in point (**2**) of 4.3.3. If during this breakthrough of washing solvent demixing occurs, the solvents will settle by density. Since the density of water (0.998 g/cm^3) is higher than the density of acetonitrile (0.786 g/cm^3), the water layer will settle towards the refractometer. The ratio of the solvent mixture will increase towards water, decreasing the measured refractive index towards the refractive index of pure water.

Batch I18DD1429 shows a deviation to the golden batch washing curve at the end of the washing process. After the water wash, a spike in refractive index is measured. This spike in refractive index is probably due to the displacement of first washing solvent, Acetonitrile/water. The max refractive index value of the spike is 1.3409. This refractive index value is close to the refractive index value measured during the Acetonitrile wash at point 6 in Figure 72. The change in the refractive index cannot be explained by an increase in concentration, as a large amount of washing solvent has been used and changes in concentrations should be minimal. Further research should be done to explain these deviations.

Batch I18DD1429 and batch I18DD1438 show a small spike in refractive index, respectively 11.7 and 16.7 min after the end of second wash. This spike in refractive index is due to the Pressurized Advanced Centrifugation (PAC), where any remaining liquid in the filter cake is forced out of the cake. The liquid is forced out of the cake using a N_2 flow of 1000 Nm^3/h.

4.3.3.2. Summary of effects and deviations Alios Crude

The deviations and effects on the refractive index washing curves are summarised in Table 37.

Table 37 Summary of deviations and effect in washing curves of Alios Crude

Effect or deviaton	Alios Crude washing
Technical washing effect	Yes
Refractive index change during washing	Exponential decrease to refractive index of solvent
Reactor washing effect	No

4.4. End point determination

End point determination of the washing based is on refractive index was done on product Alios T3728. Of this product the most amount of data was available at the time of this research. Batch I18CD0989 will be discussed as an example, as this is the golden batch of this product. As shown in the refractive index of load 1 in Figure 58, does this product show a promising simple increase of 0.0018 in refractive index. No large deviations such as spiking or sudden increases or decrease were measured during the washing. This allowed for end point determination on the refractive index of this product. No last loads will be used for end point determinations, as they show large deviations to the golden batch due to reactor washing.

During the technical wash and the first half of the normal wash, the refractive index stays constant. Halfway the normal wash the refractive index starts to increase. After the increase of 0.0018, the refractive index again becomes constant. This signals the end of the washing, as all impurities are removed and no change in refractive index is notable.

End point determination is done by calculating the first derivative of the refractive index. During the constant periods of the refractive index the first derivative will be equal to 0. When the refractive index does increase, the first derivative will also increase in value. When the refractive index starts to go back to constant, the first derivative will start to drop to 0. The drop to 0 of the first derivative after the refractive index increase, signals the end of the washing.

Figure 74 shows the refractive index on the left y-axis in blue and the first derivative (dx) on the right y-axis in orange. From the first derivative, a moving average (MA) was calculated. This was done to level out any small deviations, as the first derivative would change for every small increase or drop. A moving average of 2, 3 and 4 values of the first derivative were calculated and plotted in grey, yellow and green. Upper limit and lower limit were chosen at ±0.0006, which is 3 times the accuracy of the refractometer (±0.0002).

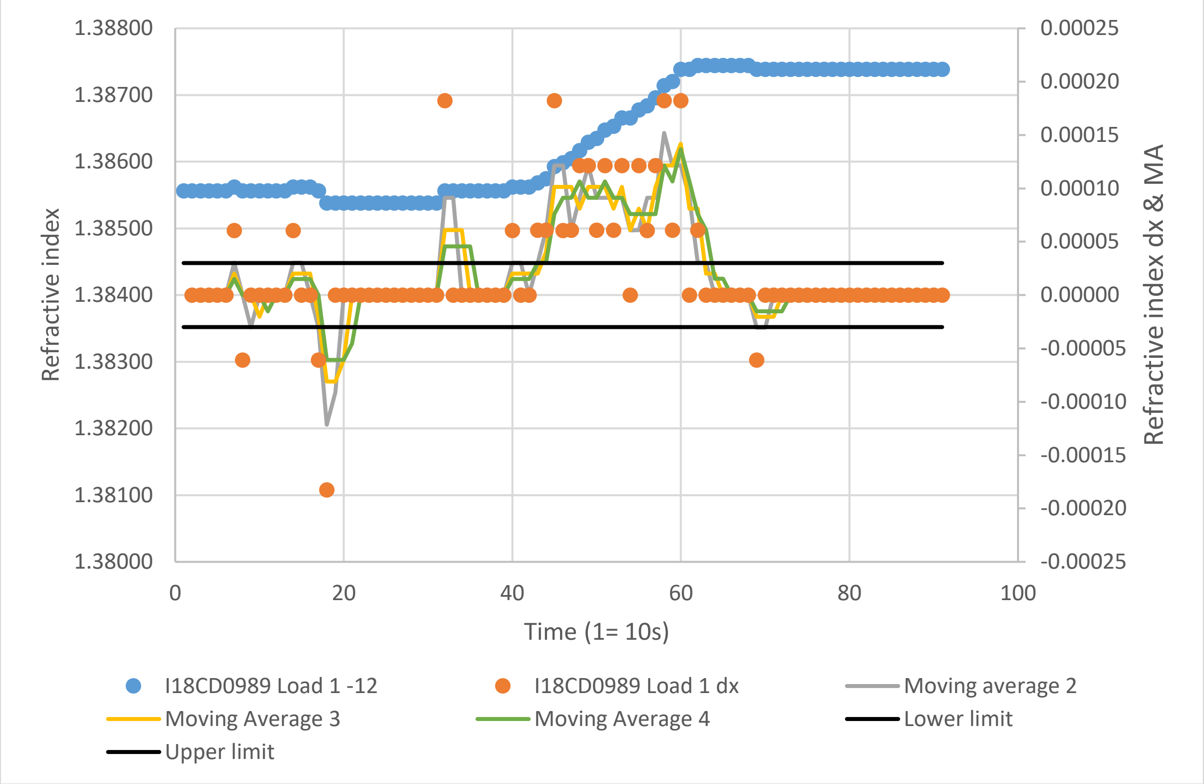

Figure 74 Batch I18CD0989 refractive index, first derivative and moving average

As shown in Figure 74 shows that after the increase in refractive index and thus change in the first derivative, the moving average goes to 0. When the moving average stays between the upper and lower limit, the end point of the washing has been reached. For batch I18CD0989 the end point can be determined with a moving average of 3 and 4, as they stay within the limit.

The moving average was calculated for every batch of Alios T3728, as shown in Table 38. The end point of each batch and each load was tested using the moving averages. If the moving average stayed within the bounds, the moving average can be used as an end point determination (Y). If the moving average exits the bounds, the moving average cannot be used for end point determination for that batch (N).

Table 38 Alios T3728 moving average

Batch	Load	End point (Y/N)		
		Moving av 2	Moving av 3	Moving av 4
I18BD0752	1	N	N	Y
	2	N	N	N
I18BD0753	1	N	N	N
	2	Y	Y	Y
I18CD0817	1	Y	Y	Y
I18CD0821	1	N	Y	Y
I18CD0926	1	Y	Y	Y
I18CD0927	1	N	N	Y
	2	N	Y	Y
I18CD0989	1	Y	Y	Y
I18CD0990	1	N	N	N
I18CD1087	1	Y	Y	Y
I18CD1088	1	N	Y	Y

The moving average with 4 values has the most loads and batches that stayed within bounds. This was expected, as the moving average with 4 values takes a larger average from the first derivative data. Any deviations are levelled out.

For batch I18CD0752 load 2, batch I18CD0753 load 1 and batch I18CD0990 no moving average stayed within the set up limits. Batch I18CD0752 load 2, batch I18CD0753 load 1 are both early batches, as they were the first batches that were produced of this product. During these early batches, a lot of process optimisation still occurred. This resulted in large changes of process parameters, resulting in larger deviations in the refractive index. Batch I18CD0990 was a bad batch, with a different crystal structure than the golden batch. This change in structure of the crystals in the filter cake resulted in a large deviation to the golden batch. The refractive index of this batch remained constant during the washing. No beginning or end could be determined.

4.5. Profit calculations

The goal of Process Analytical Technology (PAT) is gaining process knowledge, automatization and optimisation of processes. If PAT is used correctly it provides faster production times and decreased production costed due to optimisation. In the CDPP, the production processes of the API are scaled up and optimised. The focus of PAT is within the plan is mainly gaining process knowledge. This process knowledge is then used for optimisation of the process. In commercial plants the focus of PAT would mainly be increasing production and decreasing cost of production. Any decrease of cost that can be done on the level of CDPP will be significantly larger in commercial plants, since larger amounts of products are produced.

4.5.1. Reactor washing

The refractive index indicated that by doing a reactor wash in the last load, the normal wash wouldn't be necessary. Eliminating the normal wash would significantly decrease the cost of batch loads. The cost of a normal wash for each product is calculated in Table 39. The amount of washing solvent that is used in a normal wash for each product is given. Besides the cost of the normal wash, the product loss for each load is also given. The percentage loss for each load is based on the average dry weight of each last load.

Table 39 Normal washing cost and product loss for last loads

Product	Washing volume (L)	Cost washing solvent reactor wash (€)	Average last load size (kg)	Product loss (g)	Loss on load (%)
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

The cost that can be saved for the washing solvent may seem small, but this is only because of the small average load size of each batch. In commercial plants, where larger volume of product need to be produced, this will have a much larger impact.

The loss of product is even more important than the cost that can be saved on the washing solvent. Complicated API products take multiple months to synthesize and have a large cost. Each loss of product is very significant. In larger commercial plants the loss of load would also be larger, since larger loads and batches are used. The amount of washing solvent to wash the larger filter cake is increased. Because the product has a low solubility in the washing solvent, product will dissolve in the washing solvent during the washing process.

5. Conclusion

Lab tests revealed that the influence of temperature and evaporation of washing solvent on the refractive index were small. The refractive index decreases 1.8E-05 values for each 1°C increase in temperature. The refractive index of the washing solvent IPAc/Heptane (1:4 vol) increases 0.000281 when left to evaporate for 5 min. The refractive index of the washing solvent Acetonitrile/Water (1:2.5 vol) and (1:4 vol) decreases -0.001008 and -0.002133. In general, the refractive index changes towards the refractive index value of the pure washing solvent with the lowest vapour pressure. Although the effects on the refractive index were small, they still should be considered when studying washing curves for deviations. The API concentration in the washing solvent had no effect on the refractive index.

Pilot tests determined that the flow time between washing tank and refractometer through the centrifuge dryer is 76s. The influence of temperature on the refractive index, tested on pilot scale, was 4 times larger than the effect on lab scale. The refractive index decreases for 0.000423 for each 1°C increase in temperature. Increasing the rotational speed of the filtering centrifuge resulted in shorter wash times. The effect of rotational speed was only studied using a low resistance and compressible $NaHCO_3$ filter cake of 4 cm. Further research of the effect of the rotational speed on the washing time, using high resistance and compressible filter cake, should be done. The effect is expected to be smaller.

The refractive index washing curves of Alios T3728, Alios T3730 and Alios Crude were examined. All products, except for Alios T3728, showed a change in refractive index due to technical washing. Alios T3728 showed an increase of 0.0018 in refractive index during washing. There was a large difference in start and end point of the refractive index curves, which could not be explained. The reactor washing had a major effect on the refractive index washing curve, causing a large difference between first loads and the last load. High filling weights caused stretching of the refractive index curve, increasing the jump in refractive index and the washing time. There was a good correlation between the theoretical trend of the golden batch and the measured curves after selection based on deviations and process parameters. The washing curve of Alios T3730 showed differences between load 1, load 2 and load 3. This was due to the unstable crystal morphology, which changed over time. The washing curves of Alios Crude were very similar. The refractive index showed an exponential decrease in refractive index towards the refractive index of the washing solvents.

For the washing trends of the product Alios T3728 an end point could be determined, using a moving average. The reactor washing also indicated that no additional normal wash was needed. For the products Alios T3728, Alios T3730 and Alios Crude this would result in a saving of washing solvent with a cost of 243.59, 28.14 and 101.39 € for each batch. Additional to the cost saving of the washing solvents, product loss would be minimized. Not executing a normal wash after the reactor wash would increase product yield for Alios T3728, Alios T3730 and Alios Crude by 0.37, 0.46 and 1.97%.

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