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Development and Implementation of a Controlled Continuous Manufacturing Process

Solid-Liquid Separation for Pharmaceutical Production

DOCTORAL THESIS

to obtain the academic degree of

Doktor der technischen Wissenschaften

submitted to

Graz University of Technology

Supervisor

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Institute of Process and Particle Engineering

Graz University of Technology

Graz, Austria

Graz, November 2015

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Dissertation

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AFFIDAVIT

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July, 2015 .....

DI Johannes Gursch

“Hard work is only worth it in the right conditions.”

Frank Underwood

to those who provided the soil

Acknowledgement

First of all I want to express my gratitude to Prof. Johannes Khinast for the scientific supervision and for his immense fund of ideas allowing the materialization of a plentitude of projects one of which provided the basis to this work.

For financial support and for many motivating discussions I want to thank the team of Novartis Pharma AG Basel, especially Markus Krumme, Norbert Rasenack and Jörg Brozio.

Above all I want to thank Prof. Gernot Krammer for introducing a scientific phase to the process. His guidance and advice always was a valuable incentive and helped filter even the most challenging subjects.

My co-workers, friends and colleagues I want to thank for the good times at the institute and the RCPE alike as well as for their support throughout my work.

Abstract

Changing market conditions and a rapidly evolving technology landscape have caused pharmaceutical companies to relinquish traditional 'large batch' manufacturing. Continuous manufacturing is the new maxim, promising increased overall efficiency. However a large gap still exists concerning process equipment ready to cope with the challenges posed by continuous manufacturing in pharmaceutical production. Continuous small scale equipment able to treat a large variety of products, beyond laboratory solutions, is still rare, especially in the field of solid-liquid separation.

In order to evaluate and characterize promising equipment, both in the field of mechanical and thermal solid-liquid separation, representative model systems were chosen.

For mechanical separation a dynamic cross-flow filtration device was selected. Extensive experimental testing assured profound characterization and allowed to develop hypotheses to explain observed filtration behavior. A one parameter linear equation was established to allow mathematical description of filtration rates. Additionally alternative operation strategies were developed. A detailed analysis of pros and cons of each operation strategies was conducted and recommendations were given.

In the field of thermal separation five technologies apt to handle small volume streams of pre-treated, highly concentrated slurry were identified. Two fluidized bed spray dryers, a spin flash dryer, a mini spray dryer, a paddle dryer and an extruder setup were thoroughly analyzed. Trials were conducted to challenge each technology and assess strengths and weaknesses. A detailed comparative evaluation was performed to provide a sound basis for process development.

Kurzfassung

Fortschreitende Veränderungen im pharmazeutischen Marktumfeld sowie rapide Entwicklungen am Technologiesektor bewirken eine vermehrte Abkehr von der traditionellen pharmazeutischen Fertigungsweise in großen Chargen. Kontinuierliche Fertigung ist das Maxime, mit dem Ziel der Steigerung der allgemeinen Effizienz. Indes besteht in der Branche ein latenter Mangel an Prozessequipment um die Herausforderungen kontinuierlicher Produktion im pharmazeutischen Bereich zu meistern. Abseits von Laboranwendungen, ist geeignetes kontinuierlich arbeitendes Equipment, mit ausreichender Flexibilität bezüglich Durchsätzen und Einsatzfähigkeit für eine Vielzahl von Produkten, Mangelware. Insbesondere der Bereich der fest-flüssig Trennverfahren ist hiervon betroffen.

Zur Evaluierung und Charakterisierung geeigneter Systeme im Bereich der mechanischen- und thermischen fest-flüssig Trennverfahren wurden repräsentative Modellsysteme ausgewählt.

Als mechanisches fest-flüssig Trennverfahren wurde ein dynamisches Cross-Flow-Filtrationsaggregat ausgewählt. Als Grundlage zur Charakterisierung des Filtrationsverhaltens, sowie zur Validierung aufgestellter Hypothesen über zugrundeliegende Mechanismen, wurden ausführliche Versuchsreihen durchgeführt. In Folge konnte ein Ein-Parameter-Modell entwickelt werden, um die mathematische Beschreibung zu erwartender Filtrationsraten zu ermöglichen. Weiters wurden alternative Betriebsweisen entwickelt und detailliert auf deren Vor- und Nachteile untersucht. Empfehlungen zur Prozessintegration wurden in Folge abgeleitet.

Im Bereich der thermischen Separation für kleine Durchsätze konnten fünf Technologien zur Verarbeitung von vorbehandelten hochkonzentrierten Schlämmen identifiziert werden. Dementsprechend wurden zwei Wirbelschicht-Sprühtrockner, ein Spin-Flash-Dryer, ein Mini-Sprühtrockner, sowie ein Extruder in Versuchen auf deren Stärken und Schwächen evaluiert. Eine komparative Beurteilung der getesteten Technologien als Entscheidungsgrundlage für die Prozessentwicklung wurde erstellt.

Contents

"Alchemy is the art

that separates what is useful from what is not

by transforming it into its ultimate matter and essence."

Paracelsus

1. Introduction

1.1 Motivation

Pharmaceutical manufacturing is undergoing massive changes. With healthcare providers forcing pricing models to change from 'value' driven to manufacturing-cost based models, traditional, inventory heavy pharmaceutical large batch production methods have to be reviewed .[1] Even in terms of quality and repeatability pharmaceutical manufacturing, operating at 3-4 σ, lacks far behind industry norms.[1] As a consequence lengthy final product testing is required to meet the high standards required for drug products. Thereby generating high quality associated costs for failed batches during final testing.[2] Another aspect strongly impacting the pharmaceutical manufacturing landscape is a lack of new blockbuster drugs.[3] Personalized medicine is on the rise, individualizing therapies tailored to fit specific anatomical, physiological or genetic phenotypes.[4], [5] That is, a large number of new drug molecules is focusing on niche markets.[6] This however, implies a large range of production volumes with a tendency towards smaller volumes as well as an increased variety of products.[1] Thus new needs concerning production equipment arise. Increased production efficiency, ability to handle small production volumes and high flexibility in terms of treatable products is required. All of these needs can be addressed by the introduction of continuous manufacturing technologies. Benefits associated with the introduction of continuous manufacturing are discussed in chapter 0, 0 and 0.

Worldwide the pharmaceutical industry has already spend over £1 billion into the development of continuous manufacturing processes.[7] An expected amount of over £100 million have been spend, per company, on research projects concerning continuous manufacturing.[7] Institutions like, e.g. Novarits-MIT Center of Continuous Manufacturing but also collaborations projects like the EPSRC Centre for Innovative Manufacturing in Continuous Manufacturing and Crystallization have been founded. Intensive research is undertaken addressing upstream tasks like crystallization, [8]–[11] however, development of downstream operations addressing solid-liquid separation tasks is still scarce. Solid-liquid separation includes inter alia mechanical solvent removal as well as thermal drying, both processes symbolizing crucial steps in pharmaceutical manufacturing. [12] Whilst large scale continuous equipment for solid-liquid separation is already widely implemented in the chemical industry and those can be bought off the shelf, [13] there is still a significant lack of continuously operating small scale equipment. This work strives to close this gap by identifying equipment ready to use for industrial application. This work contributes to the applied research conducted in the area of process development for continuous manufacturing in the pharmaceutical industry.

1.2 Solid-liquid separation[1]

Reduction of product moisture or solvent content below a certain limit is a crucial process step during pharmaceutical manufacturing. Reasons for moisture or solvent removal are to [14]:

- obtain free-flowing material to facilitate transport, dosing or packaging
- to enable subsequent manufacturing steps, e.g., direct compaction

[1] Parts of this section are to some extent based on section 5 "Drying", which was written by the author of this thesis, of the book chapter: S. Sacher, J. G. Khinast, "An Overview of Pharmaceutical Manufacturing for Solid Dosage Forms," in "Continuous Manufacturing of Pharmaceuticals", John Wiley & Sons, Ltd, submitted.

- to remove toxic solvents and to ensure minimal impurity levels in the final drug product
- to create a certain morphological structure, e.g., an amorphous material
- to guarantee long-term stability by prevention of hydrolysis or other reactions
- to extend shelf-life by prevention of mildew and bacterial growth

Even if the final drug product is not a solid dosage form, a solid-liquid separation step might be required for one of the above given reasons or simply in order to produce an intermediate product.

To achieve separation in general, three basic mechanisms can be distinguished: separation by phase transition (achieved by energy supply or removal), separation by phase affinity (achieved by mass agent removal or supply) and mechanical separation. Separation by phase transition as well as separation by phase affinity is based on molecular driving forces governed by thermodynamic equilibrium. Whilst for mechanical separation mechanical impacts, e.g. centrifugal forces are implemented.[15]

During mechanical solid-liquid separation achievable residual moisture or solvent concentrations are often above critical boundary values, therefore, thermal processes can be very energy consuming and those cost intensive. Apart from this, stability issues, mechanical as well as thermal stability of the treated substances, play an important role when choosing appropriate soli-liquid separation processes. Combinations of mechanical as well as thermal processes are very common. For example, to keep energy consumption low it is generally advisable to mechanically remove as much of the solvent as possible before thermal drying, [16]–[18] i.e., by filtration.

In the following sections especially thermal solid-liquid separation, as prominent process using phase transition as separation method, and filtration, as a commonly used technology based on mechanical separation principles, will be addressed. Membrane filtration processes where selective barriers are used to achieve sepa-

ration according to physical and chemical properties as example for separation processes based on phase affinity will be mentioned marginally in chapter 1.3.

1.3 Mechanical solid-liquid separation (MSL)

Mechanical solid-liquid separation describes processes where liquid and solid phases are separated by mechanical means. To assure optimal process design, mechanical solid-liquid separation processes are usually located upstream of thermal separation processes.[18]

1.3.1 MSL Fundamentals

The chief mechanical means implemented to achieve solid-liquid phase separations are sedimentation, expression and filtration.[19] In sedimentation body forces, e.g. gravity and centrifugal forces are used to achieve separation.[20] Expression is achieved by compression of sludges.[21] Filtration describes the process of separation of solid particles from a liquid phase by means of a filter medium. Whereas the liquid phase permeates the filter medium solid particles are held back. A pressure gradient acts as a driving force for flow through the membrane.[21]

Depending on the application either liquid phase or the solid phase may be the desired product. Achieved separation is always incomplete. That is, some solids might still be present in the permeate, so called turbidity, and the retentate often exhibits relevant levels of residual moisture, caused by liquids adhering to the solid phase.[21] Therefore additional washing steps are often needed during pharmaceutical processing. This can lead to a sequence of several filtration and dilution or washing steps, e.g. to remove toxic solvent or complete exchange of mother liquid in order to avoid precipitation or other unwanted reactions during follow up manufacturing steps.

Mechanical solid liquid separation processes can be classified according to the following four criteria [21], [22]:

- *Location of particle retention:* A distinction can be made between deep bed filtration and surface filtration. In deep bed filtration particles are collected within the filter medium itself. Deep bed filtration is usually applied for very low feed concentrations, allowing particles to pass unhindered into the pores of the filter membrane.[23]

  Surface filtration encompasses cake-, cross-flow- and cake filtration.[18] In cake filtration particles larger than the pore size of the filter medium are retained on the filter medium. This sieving process leads to the formation of a filter cake. Smaller particles can be retained by the filter cake itself or through formation of bridge like agglomerates over a pore entrance of the filter medium.[23] Subsequently post treatment steps such as cake washing, desaturation or compression are common.[18]

  In cross-flow filtration a tangential suspension stream is used to prevent cake formation. That is, shear is applied to remove potential cake or concentration polarisation layers. Suspensions can be concentrated up to their flowability limit. Cross-flow filtration is used to separate very small particles and highly dilute suspensions. In such cases cake filtration would be uneconomically due to high filter cake resistances or long filtration times.[18]

  Blocking filtration is also applied for separation of highly dilute suspensions. In blocking filtration gradual blockage of filter media pores is allowed. To avoid transgression of a critical pressure loss limit, mechanisms to remove blocking particles have to be implemented, e.g., back flushing. [18]

- *Pressure gradient generation:* Gravity, Vacuum, Pressure or centrifugal forces might be applied as driving force for the separation process.[21]

- *Operation mode:* Filtration equipment can be operated in continuous- ,batch- or semi continuous mode. A further distinction can be made in static or dynamic filtration. In dynamic filtration the build up of a filter cake is reduced by means of adequate process mechanism, such as propellers or a moving filter surface (dynamic cross-flow filtration).[24]

– *Particle size:* Membrane filtration processes can be classified according to the size of the separated substances and the applied pressure. Microfiltration (>100 nm; 1-4 bar), ultrafiltration (4-100 nm; 5-10 bar), nanofiltration (1.2-12 nm; 20-40 bar), reverse osmosis (0.5-1.5 nm; 30-60 bar). Throughout this processes membranes are usually applied as filter medium, with the exception of microfiltration and ultrafiltration where, e.g. woven fabrics or wire cloths are also commonly used.[22], [24] In such cases separation by mechanical means is achieved. However, when processing smaller particles such as molecules, ions, etc. thermodynamic parameters are predominant and separation is achieved by phase affinity.

1.3.2 MSL equipment

As depicted in Table 1 a large variety of equipment exists on the market to meet with the multitude of demands posed by industrial applications. Detailed analyses of the mentioned equipment types are presented elsewhere.[15], [18]–[21], [25]–[27]

Table 1 Overview and classification of common equipment for mechanical solid-liquid separation [25]

Gravity filtration	Vacuum filtration		Centrifugal filtration
Batch:	Batch:	Continuous:	Baffle ring centrifuge
Single leaf nutsche	Multi element leaf	Horizontal belt	Basket centrifuges
Semi-continuous:	Single leaf nutsche	Horizontal rotary table	Cone screen centrifuges
Sand bed	Single leaf tilting pan	Horizontal tilting pan	Inverting bag centrifuge
Continuous:		Precoat rotary drum	Screen baffle centrifuge
Gravity belt		Rotary disc	Single and multi-stage pusher
Stationary screen		Rotary drum bottom fed	
Vibration screen		Rotary drum top fed	
		Rotary drum internal fed	

Pressure filtration			
Batch:	Semi-continuous:	Continuous:	Variable volume:
Multi-element candle	Bag	Belt press	Diaphragm filter press
Multi-element leaf	Cartridge	Duplex strainer	Expression (screw) press
Plate & frame press	Dead-end membrane	High shear cross-flow	Horizontal element tube press
Precoat nutsche & multi-element leaf	Fibre bed	Rotary disc	Vertical diaphragm filter press
Precoat plate & frame press	Low shear cross-flow	Rotary drum	Vertical element tube press
Recessed plate filter press	Sand bed	Sand bed	
Sheet filter	Simplex strainer	Tower press	
Single leaf nutsche			

Gravity sedimentation	Centrifugal sedimentation	Force field
Circular thickener	Disc stack centrifuge	Combine field
Deep cone thickener	Scroll decanter centrifuge	High gradient dielectrophoretic
Lagoon thickener	Single and multi-bowl basket centrifuges	High gradient magnetic
Lamella separator	Tubular bowl centrifuge	High intensity magnetic
Settling tank thickener	Circulating bed hydrocyclone	Low gradient electrical
Blanket clarifier	Reverse flow hydrocyclone	Low intensity magnetic
Inclined plate clarifier		Ultrasonic assistance
Rectangular clarifier		
Vertical flow clarifier		
Helical screw classifier		
Hydraulic classifier		
Rake classifier		
Flotation		

In the course of this work the main focus concerning mechanical solid-liquid separation equipment was on dynamic cross-flow filtration. In classical cross flow filtration shear is generated by tangential flow of the suspension to be concentrated over the filter media. Shear rate increases are achieved either by increasing flow velocities or decreasing tube diameters or channel thickness, creating axial pressure gradients. This necessitates not only the use of energy intensive feed systems but also leads to suboptimal utilization of membrane surface alongside the filter axis. In dynamic

cross-flow filtration this problem is addressed by creation of shear rates by rotating parts.[28], [29] Methods applied to achieve such a decoupling of shear rates from inlet flow rates are shown in Figure 1.

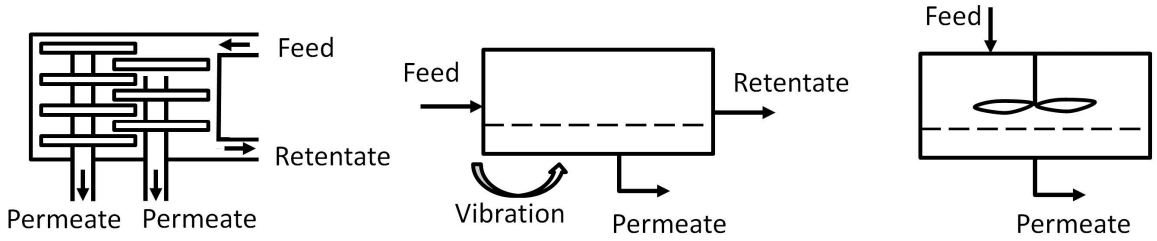

Figure 1 Dynamic cross-flow filtration principles (from left to right): rotating cylindrical systems, rotating disk systems, vibrating systems, systems with integrated stirrers [18], [28]

- *Rotating disk systems:* In this type of systems shear is generated by rotating the filter media itself. Use of intermeshing disk stacks not only allows to increase membrane area but also enhances shear rates in overlapping regions. Alternative approaches not only rotate the filter media around their central axis but add additional movement by revolving the membrane disk stacks around a central axis. Intermeshing disk systems risk membrane breakage at elevated viscosity levels, as concentration polarization layers might establish and lead to blockage of the rotating disks.

- *Vibrating systems:* Vibrating systems are often implemented for treatment of shear-sensitive materials. These systems are very energy-efficient however maximal achievable viscosities are rather low, as they are prone to membrane blocking for high viscosity suspensions.

- *Systems with integrated stirrers:* Systems using rotating elements in front of a stationary filter medium, offer high shear and promise enhanced capabilities concerning treatability of highly viscous suspensions. A multi-chamber system using rotors is shown in Figure 2.

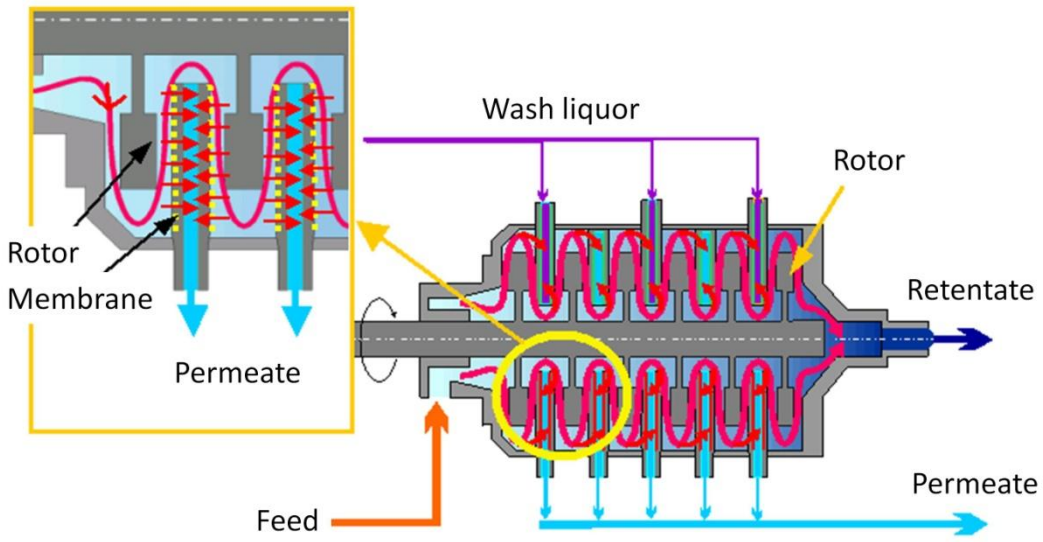

Figure 2 Modular multi-chamber dynamic cross-flow system Bokela DYNO© Filter [30]

1.3.3 MSL selection procedure

As throughout every design phase, final product requirements (regulatory requirements, purity, residual moisture, etc.) as well as equipment and operation properties (efficiency, integration with follow up steps, flow rates, etc.) have to be considered. Generally theoretical evaluation suffices to fully address the points mentioned. However, to connect suspension property data (particle form and size distribution, porosity, viscosity, etc.) to process related properties (sedimentation behavior, cake resistance, washing behavior, etc.), screening tests have to be performed.[27]

Lab screening tests are used to determine e.g. settling rate, clarity of supernatant liquid, final proportion of sludge, agglomeration properties, etc. Especially cake formation tests, as extensively described in chapter 0, are very often performed in the industry in order to determine relevant process related date such as cake resistance, residual moisture values, tendency to crack formation, etc.[19], [23], [26]

Several systematic approaches exist to connect the generated data with the most appropriate separation equipment [31]:

– Non-ranked tables: Optimal equipment choices are listed depending on characteristic parameters, such as cake resistance, cake formation time and particle size. An example of such a list is shown in Table 2.

Table 2 Suitable equipment depending on cake formation rate [19]

Cake formation rate	Suitable equipment
0.1-10 cm/sec	Gravity pans, belt-, top feed drum filter, pusher centrifuge
0.1-10 cm/min	Vacuum drum-, disk-, belt filter, peeler centrifuge
0.1-10 cm/h	Pressure filter, disk-, tubular-, sedimentation centrifuges
Negligible cake	Cartridges, precoat drums, filter aid systems, deep bed filters

– Ranked tables: Equipment performance is evaluated and scored in order to produce a ranked list. A graphical illustration of the information presented in a ranked table is shown in Figure 3.

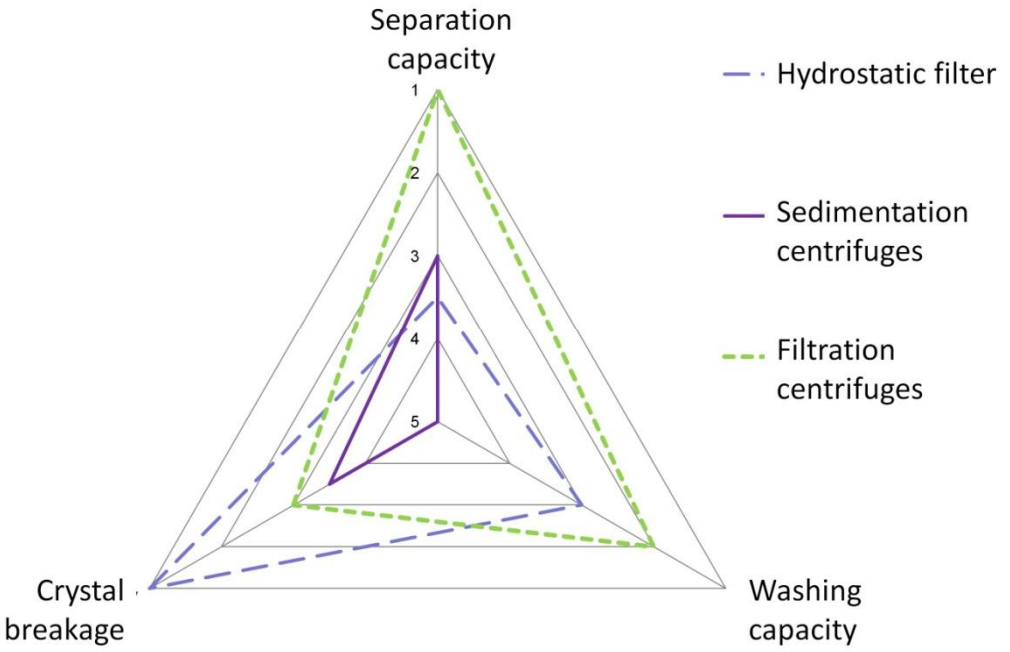

Figure 3 Graphical illustration of the information presented in a ranked table. Three technologies are evaluated according to their performance concerning separation capacity, risk of crystal breakage and washing capacity (one...very good, five...insufficient)

- Decision trees: A structured selection process is proposed by following a tree-like graph as shown in Figure 4. Each intersection of the graph depicts a logic decision point. By following through the decision strands the user is guided to the most appropriate equipment.

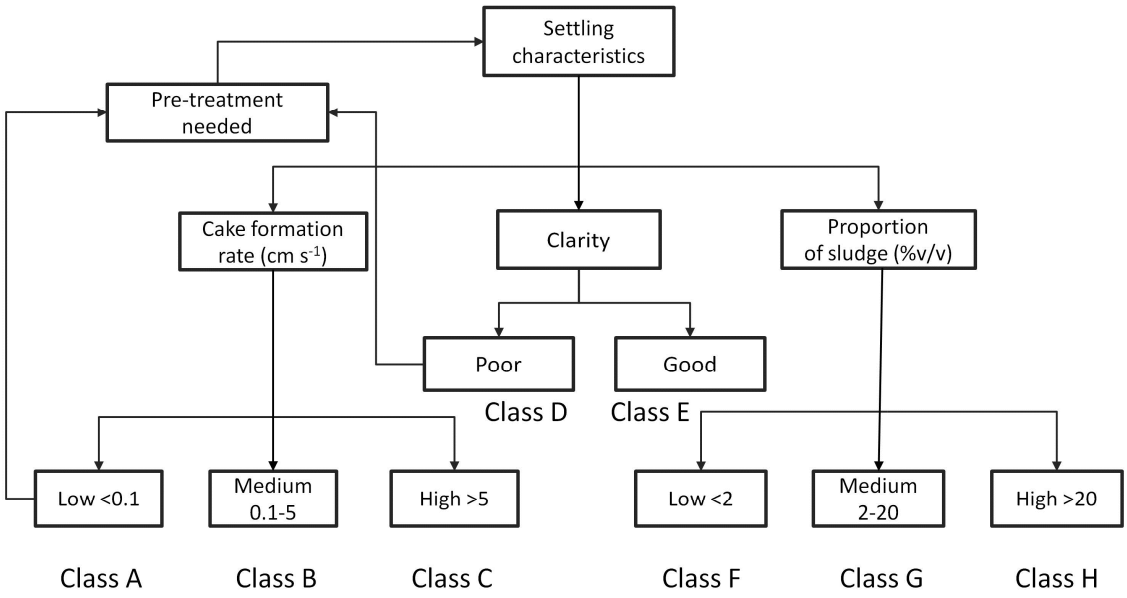

Figure 4 Decision tree as structural approach to select a generic equipment class based on settling characteristics [23]

- Software aided selection: Relevant parameters (product requirements, equipment and operation properties suspension property data process related properties) are fed to a computer program. The implemented rule based expert system subsequently selects and ranks the most suitable equipment automatically. [32]

1.4 Thermal solid liquid separation (TSL)[2]

Thermal solid-liquid separation describes processes where liquid and solid phases are separated by phase transition due to energy supply or removal.[15] TSL usually follows steps such as crystallization/filtration/washing, wet granulation or wet extrusion, but is also used to create particles of a desired morphological structure (e.g., spray drying).

1.4.1 TSL fundamentals

TSL or drying of material is a complex process, its intricacies often being underestimated. For example, during drying of a porous material, several processes are occurring at the same time. Consider a porous pellet: First heat and mass-transfer occur at the external gas-solid boundary layer of the particle. Second, in the internal pore space liquid and gas phases exists that exhibit complex transport phenomena of the gaseous components, liquid phase and heat. Moreover, a local equilibrium between the liquid phase and the gas phase exists, which in the case of free liquid water is described by the vapour pressure, but at low moisture contents becomes an adsorption isotherm. Thus, the temperature and humidity of the drying air has a large impact on the process.

All these effects can under certain conditions become rate-limiting, leading to "drying regimes". The most common regimes include the "constant-rate period" at high liquid content, where the drying rate of a porous pellet stays constant due to limitation by the external heat transfer. In this case the material is rather cool, maintaining the so-called "wet-bulb temperature". Once the transfer of liquid to the surface of the pellet becomes rate limiting, the "falling-rate period" is observed at low moisture contents, with a constant reduction of the drying rate. Inside the pellet strong temperature and

[2] Parts of this section are to some extent based on section 5 "Drying", which was written by the author of this thesis, of the book chapter: S. Sacher, J. G. Khinast, "An Overview of Pharmaceutical Manufacturing for Solid Dosage Forms," in "Continuous Manufacturing of Pharmaceuticals", John Wiley & Sons, Ltd, submitted

concentration gradients develop until the material is dry. Note, however, that in addition to heat and mass transport also a redistribution of the API in the pellet or swelling/shrinking behaviour of the porous substance may occur.[2, 3] Drying of non-porous substances involves only a constant-rate period. During drying also precipitation and/or crystallization of dissolved materials may occur, e.g., during spray drying. In the latter process, removal of solvent is typically fast, such that amorphous materials are obtained.

Models used to describe this complex process range from global heat and mass balances to detailed incremental methods, tracking local conditions of solids and gases throughout the drying process. Mechanistic, first-principle based models allow exact predictions over a wide range of process conditions. However, detailed rigorous models often demand a large number of parameters that difficult to obtain. Therefore, lumped parameter models and simple correlations are often used as an alternative.[35] [36]

In general, drying, implying heating and evaporation (or vacuum generation), is highly energy consuming. Moreover, wet powder needs to be agitated in some form, to increase heat and mass transfer. This, however, may lead to agglomeration and/or attrition. Therefore, choosing the most efficient drying system in accordance to product requirements and integration into previous and subsequent manufacturing steps is an important task.

1.4.2 TSL equipment

For pharmaceutical production a large number of dryers has been developed, both batch and continuously operated. Reasons for the variety in drying equipment are [14]:

- Large variations in drying kinetics: kinetics strongly depend on system properties, such as type of moisture-material bonds (e.g., free, adsorbed vs. inclusion in the crystal lattice), particle size and shape, porosity, pore size, etc. [37]

- Large variations in product requirements: specific dryer types or modes are required to achieve desired product structures, forms or shapes, or must accommodate sensitive materials or sticky powders
- Large variety of materials: As suggested in [37] pharmaceutical products can be roughly classified into moist, free-flowing granular materials and powders, paste-like materials and liquids (solutions and suspensions). Thus, materials range from filter and centrifuge cakes to granules, single moist particle assemblies, pastes, solutions or suspensions.

A classification of dryer types can be made according to the underlying mechanism of heat transfer. Accordingly, three major classes exist, including *conductive, convective* and *radiative* drying. However, in practice always combinations of several heat transfer mechanisms within one drying equipment are common.[14] Also widespread are filter-bed dryers, allowing for initial filtration and washing steps prior to thermal drying. That is, mechanical dewatering and thermal drying can be realized in one single device.[38], [39]

1.4.2.1 Convective dryers

In convective dryers heat is supplied via a gaseous phase. The gas also serves as carrier for the evaporated liquid. If inert drying gases are used or valuable solvents need to be recovered, closed cycle systems for the gas circulation are employed.[37] Most common dryers of this class are spray dryers, (spin-) flash dryers, fluidized bed dryers or belt dryers.

- *Spray dryers:* In spray drying, liquids or suspension are disperse into small droplets by means of an atomizer. This is the main challenge of spray drying, i.e., to generate a homogenous spray with a narrow droplet-size distribution even for suspensions with higher solids content. The droplets are subsequently dried in a hot air stream while falling down a spray tower. The large surface area of the formed droplets enables rapid solvent evaporation (30 - 160 $kgh^{-1}m^{-2}$ of particle surface area). In the co-current drying mode, where hot air is

injected close to the atomizer, overheating of the drug product is avoided, as the heat of the drying gas is consumed by evaporation. [37] Spray drying enables a strong influence on the final physical morphology of the drug product, e.g., by creation of amorphous phases, or certain particle sizes and shapes (spherical, hollow, etc.). That is, drug stability and release characteristics can be designed by choosing specific process parameters, such as drying gas flow rate, temperature or droplet size.[40]–[42] A schematic is shown in Figure 8. Thus, spray drying is more often used as a tool for particle engineering rather than a drying technology.

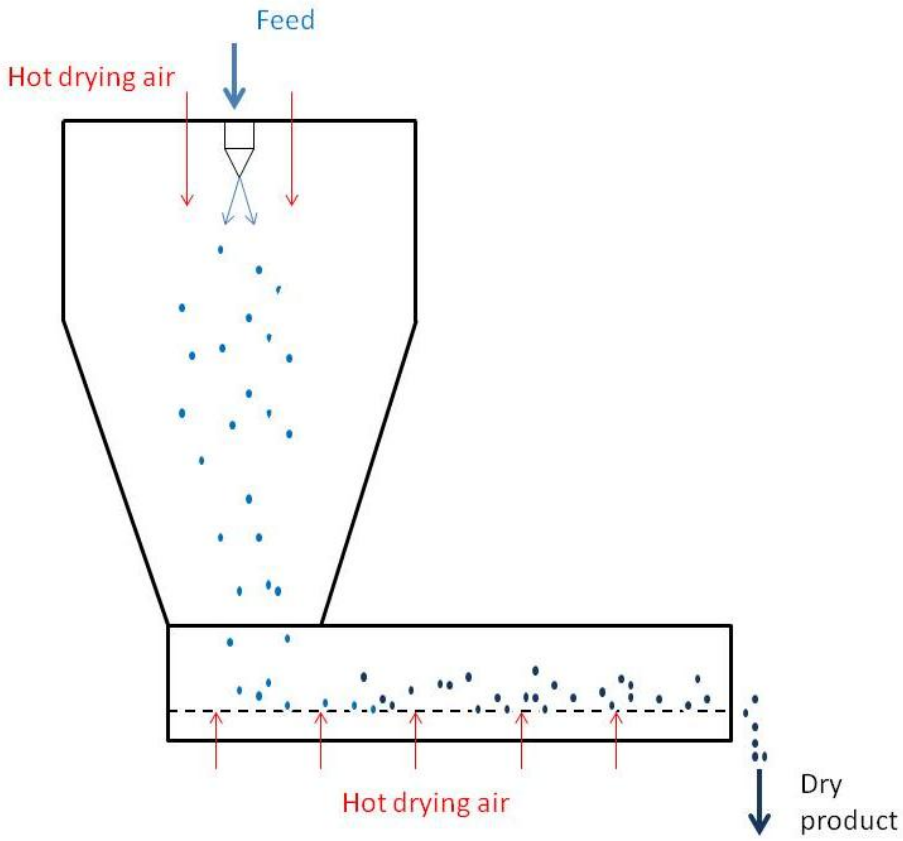

Figure 5 Schematic of a spray dryer with integrated fluid bed

– *Flash dryers:* In flash drying easy to disperse, free-flowing material is introduced into an upward-flowing drying air stream. The drying air stream also acts as transport medium for the product. This co-current drying mode and very high evaporation rates (200 - 1200 $kgh^{-1}m^{-2}$) prevent the materials from overheating.[37] A variation of this dryer type is a spin-flash dryer that also al-

lowing pasty material to be dried by providing intense agitation by blades at the bottom of the dryer (see Figure 9). Note however, that particles must be removed from the drying air stream, typically via cyclones. Thus, some particles, mostly smaller ones, are lost in the process. Flash dryers can be operated continuously.

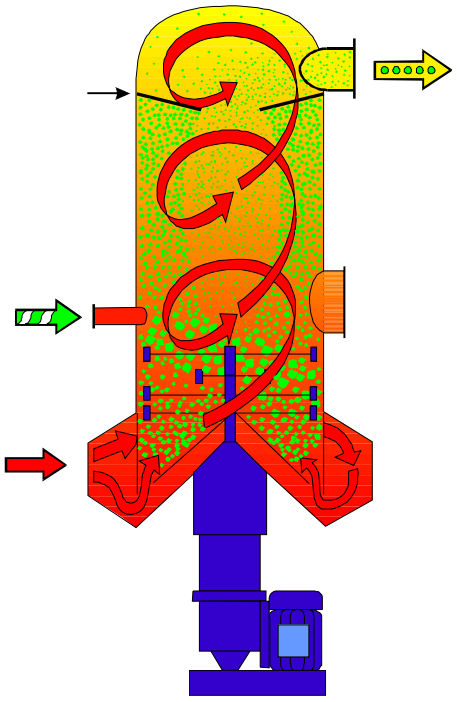

Figure 6 Schematic of a spin flash dryer [43]

– *Fluidized-bed dryers:* In fluidized-bed dryers materials are dispersed and dried in an air flow creating a fluidized particle bed with liquid-like properties. In contrast to flash dryers the particle bed is much denser and the system is operated below the particle-entrainment gas velocity, i.e., particles remain in the bed. Heat and mass transfer, as well as mixing characteristics, are very good. This dryer type can process fluidize-able granular materials with mean sizes ranging roughly from 10 microns to 1 cm,[44] with particles ranging from 25 - 1000 microns being best suited for smooth fluidization [44] based on Geldart's classification for A and B powders.[45], [46] A variety of this process is fluidized bed granulation and fluidized bed spray coating, where in addition to drying coating and granulation are performed. Fluidized-bed drying is a batch process. However, segmented fluid beds have been developed where particles

move (or are moved) through segments, such as the GEA and Glatt systems, emulating a continuous process.

- *Belt dryers:* In belt dryers the product is as evenly spread as possible on a permeable belt conveyer and continuously moved through a drying chamber where hot air dries the product on the belt.[47] Radiation drying elements (IR) can be implemented to enhance the drying effect. Problems are associated with agglomeration due to the lack of shear forces acting on the agglomerates. In addition, cleaning and validation are complex. Belt dryers are continuous systems. A schematic of a belt dryer with multiple conveyer belts for large throughput and a long residence time is shown in Figure 10.

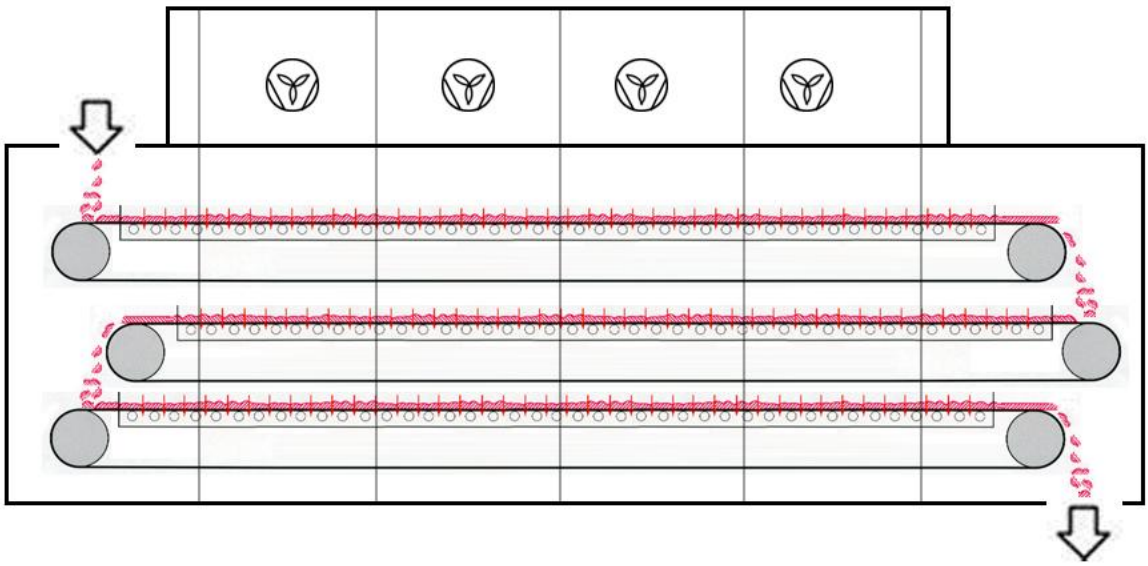

Figure 7 Schematic of a belt dryer with multiple conveyor belts for large throughput s and long residence time

1.4.2.2 Conductive dryers

In these dryers, heat is supplied via contact drying. An additional gas stream may serve as carrier for the evaporated phases. Examples for conductive dryers are drum dryers, vacuum dryers, freeze dryers, which are typically operated in batch mode:

- *Drum dryers:* In rotating drum driers usually liquids and pastes are dried, forming a layer on the dryer walls. Blades are used to scrape off the dried product. Residence time distribution, as well as energy consumption are kept low.[48] This dryer type is often used for sticky materials that would be difficult to dry using other process technologies.[37]
- *Filter(-bed) dryers:* In filter dryers the slurry (typically washed crystals) is charged and then, filtration takes place, followed by contact drying. Thus, the following steps are included: slurry charging, pressurised filtration, controlled heating and cooling, cake smoothing and drying, discharging and sampling, Clean-In-Place (CIP). A filter dryer consists of a main insulated jacketed vessel and filtration base which can be lowered for inspection and replacement of the filter media.
- *Vacuum dryers:* These driers allow solvent removal at relatively low temperatures due to decreased ambient pressure. They are widely used to dry thermolabile or easily oxidizing products.[37]
- *Freeze dryers: F*reeze drying (lyophilisation) is a multi-stage process. In a first phase low process temperatures lead to crystallization of the solvent [49] below its triple point, the lowest temperature at which the solid and liquid phases of the material can coexist. This ensures that sublimation rather than melting will occur in the following steps. Then, during the primary drying phase, the pressure is lowered (to the range of a few millibars) and enough heat is supplied for the solvent to sublime.[50] Due to low drying temperatures and the absence of air, product damage caused by oxidation and chemical modification is avoided. A possible secondary drying phase aims to remove adsorbed water molecules. This part of the freeze-drying process is governed by the material's adsorption isotherms. In this phase, the temperature is raised higher than in the primary drying phase, and can even be above 0 °C. The original properties of pharmaceutical- and biopharmaceutical products are preserved. Furthermore, freeze-dried products often exhibit extended long-term storage stability.[51]–[54]

1.4.2.3 Radiative dryers

Energy is transported directly to the material via radiation. Heat is generated simultaneously at the surface, as well as inside the material. The following systems are commonly used:

- *Microwave dryers:* Applicability of microwave driers strongly depends on the materials dielectric properties.[55] The most important factors affecting the drying rate are material properties and the wetness of the material, i.e., wet areas experience greater heating. This yields almost uniform moisture levels within the final drug products.[56] However, due to volumetric heating temperature control in the product is difficult, in contrast to hot-air drying where the drying temperatures cannot exceed the drying air temperature. Rapid local heat and mass transport can lead to deterioration of the final product quality. To overcome non-uniform temperature distributions and due to a limited penetration depth microwave drying is often combined with other conventional dryer types, i.e., microwave assisted air drying, microwave assisted freeze drying etc.[57]
- *Infrared dryers:* Infrared dryers have proven to be very energy efficient. However, radiation ranges should be adapted to the material's maximum absorption ranges.[58] External agitation of the material is often needed due to the limited penetration depth of infrared radiation. Yet, the simplicity of infrared equipment allows easy integration in convective, conductive or other radiation based systems. The high versatility of the equipment, as well as fast transient responses, make infrared dryers interesting for pharmaceutical production.[59] A schematic is shown in Figure 8.

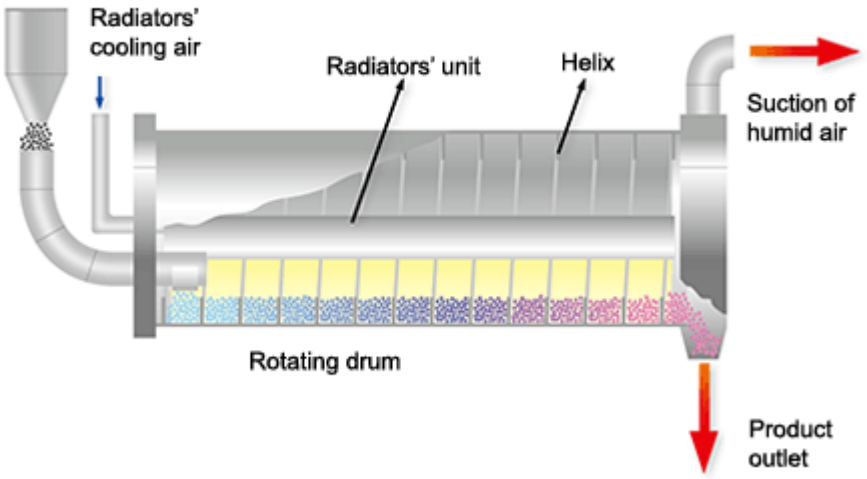

Figure 8 Schematic of an Infrared rotary drum process [60]

1.4.3 Future perspectives in TSL

With continuous manufacturing increasingly used in pharmaceutical production, continuous dryers are of significant interest. However, few systems exist that can be used for low-throughput materials in the order to 1-50kg/h. Moreover, dryers typically lead to agglomeration and/or attrition of materials which is typically undesirable .[61], [62] Moreover, for smaller particles (<30 micron) fluid bed drying is not an option. Such materials must thus be dried using other systems, such as belt driers, which may lead to caking. Thus, the implementation of novel and continuous low-throughout drying technology would be of significant interest to pharmaceutical manufacturing. A through analyses of equipment available on the market is presented in chapter 0.

For automated continuous production not only new equipment and extensive process understanding are necessary, but also process analytical tools (PAT) for drying endpoint control. With residual solvent or moisture contents being a crucial quality attribute in downstream manufacturing online tools for measuring the solvent content are very important. As an example of recent developments in this field electrical capacitance tomography used to survey moisture distributions inside fluidized bed reactors can be mentioned [63], [64] as well as spectroscopic methods (NIR).

1.5 Thesis Content

The thesis deals with the identification and characterization of small scale equipment capable of closing the technology gap in the field of mechanical- and thermal solid-liquid separation for continuous manufacturing in pharmaceutical production.

Chapter one introduces the framework upon which this thesis is based on. Justification for solid-liquid separation in pharmaceutical manufacturing is given and an overview of existing solid-liquid separation technology is presented. Fundamentals of mechanical and thermal separation processes are introduced together with concepts of categorization. Furthermore an overview of systematic approaches to facilitate equipment selection procedures as well as an outlook on future developments in the field of drying is given.

Chapter two presents a detailed analyses of the implementation of cake formation tests as crucial lab screening test during the design phase of mechanical solid-liquid separation equipment. The influence of suspension properties originating from particle as well as solvent properties on the filtration process is discussed as well.

Chapter three encompasses characterization experiments as well as hypotheses to explain underlying effects leading to the observed filtration behavior of a continuous cross-flow filtration device. Experimental validation for the developed theory is presented as well as a basic one-parameter linear equation to predict filtration behavior.

Chapter four addresses the need for increased efficiency during cross-flow filtration. Possible operation strategies are developed and advantages and drawbacks of each strategy are analyzed in detail.

In chapter five different small scale drying technologies are presented and their readiness to cope with challenges and regulatory demands arising during pharmaceutical manufacturing is examined. A comparative evaluation of the tested equipment completes this chapter.

Chapter 6 provides a summary of the major findings as well as an outlook, giving insight to further steps necessary to enable industrial application of the developed processes.

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2. Lösungsmitteleinfluss auf das Filtrationsverhalten organischer Feststoffpartikel[3]

2.1 Kurzfassung

Zur Auslegung technischer Filtrationsanlagen ist es wichtig vorab die wesentlichen materialabhängigen Prozessparameter zu bestimmen. Neuere Ansätze versuchen hierbei, neben den klassischen Kenngrößen wie z.B. die Partikelgrößenverteilungen weitere Faktoren wie den Einfluss des Lösungsmittelsystems auf die zu erwartenden Kuchenwiderstände mit zu berücksichtigen. Die verfügbare Literatur beschäftigt sich jedoch weitestgehend mit Suspensionssystemen aus anorganischen Feststoffen. Mittels eines Druckfilterversuchs nach VDI 2762_2 soll die Anwendbarkeit der etablierten Theorien auf organische Stoffsysteme überprüft und validiert werden. Erste Ergebnisse zeigen, dass im Speziellen der Zusammenhang zwischen der Benetzbarkeit und Hydrophobizität organischer Feststoffe und die daraus resultierenden Kuchenwiderstände und –höhen deutlich erkennbar ist.

[3] This chapter is based on: J.S. Gursch, D. Dujmovic, J.G. Khinast, J. Brozio, M. Krumme, N. Rasenack "Lösungsmitteleinfluss auf das Filtrationsverhalten organischer Feststoffpartikel", Proceedings of Minisymposium Verfahrenstechnik 2012, Linz

2.2 Einleitung

Bereits 2007 wurde von Peuker und Neubauer die Notwendigkeit aufgezeigt, die etablierten Theorien zur Auslegung von Filtrationsprozessen um eine weitere Einflussgröße, nämlich das Lösungsmittelsystem zu erweitern [1]. Die durchgeführten Untersuchungen zur Beschreibung des Suspensionsverhaltens nichtwässriger Systeme wurden laut Literatur hauptsächlich mit anorganischen Partikeln vorgenommen.

Im pharmazeutischen Bereich sind jedoch vor allem organische Stoffe als Wirkstoffe (API) von Bedeutung. Die in dieser Arbeit beschriebenen weiterführenden Untersuchungen wurden durchgeführt, um die von Peuker und Neubauer aufgestellten Thesen auf deren erweiterte Gültigkeit für organische Feststoffpartikel in wässrigen und nichtwässrigen Suspensionen zu überprüfen.

2.3 Equipment und Materialien

Der in diesem Projekt verwendete Versuchsaufbau, in Abbildung 1 dargestellt, besteht aus einer Druckfilternutsche der Firma Andritz KMPT GmbH entsprechend der VDI Richtlinie 2762 Blatt 2 mit einer Filterfläche von 30 cm^2.

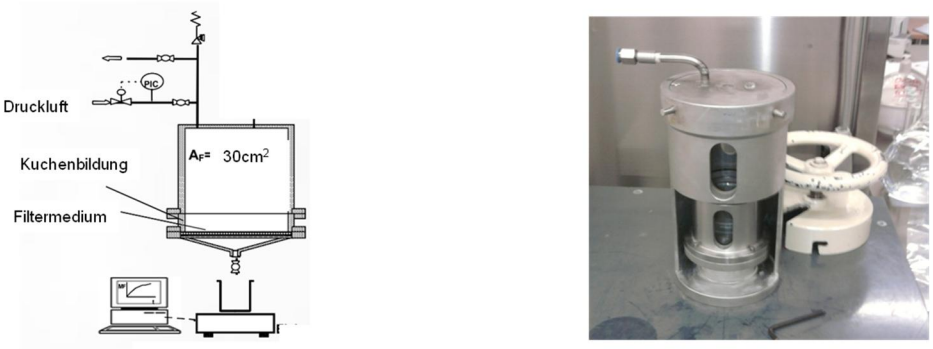

Abbildung 1 Druckfilternutsche nach VDI 2762 - Schematische Darstellung und Laboraufbau [2]

Die Erfassung des Filtratanfalls über die Zeit erfolgt mit einer Laborwaage der Firma Denver Summit Modell SI – 4002A. Die Schrittweite liegt bei diesem Modell bei 10mg, eine Auslesung erfolgt jede 0,1 Sekunden.

Da im Dauerbetrieb im pharmazeutischen Sektor die zuverlässige Reinigung der Filtermedien eine wesentliche Rolle spielt, kommen vielfach monofile Gewebe zum Einsatz. Die Filtration erfolgt deshalb mit Sefar Tetex Mono Geweben aus Polypropylen mit Maschenweiten von 8 µm bis 53 µm je nach Korngrößenverteilung der untersuchten Feststofffraktion.

Um praxisrelevante Ergebnisse zu erhalten, wurden vor allem organische Stoffe ausgewählt, die im pharmazeutischen Bereich zum Einsatz kommen (siehe Tabelle 1).

Tabelle 1 Verwendete Modellsubstanzen

Modellsubstanz	x_{50} [µm]	Partikelform
Laktose	7	kubisch/sphärisch
Ibuprofen	5	kubisch/sphärisch
Ibuprofen	34	kubisch
Koffein	29	nadelförmig

Als Lösungsmittel wurden Wasser, Isopropanol und n-Hexan festgelegt. Zur Verbesserung der Dispergierbarkeit wurde zum System Ibuprofen/Wasser ein Tensid zugegeben.

2.4 Experimentelle Durchführung nach VDI 2672

Die betrachteten Suspensionen werden nach dem Aufrühren in die Drucknutsche überführt und mit 3bar drucküberlagert. Auf der Waage wird der Filtratanfall über die Zeit erfasst. In die Drucknutsche integrierte Schaugläser ermöglichen eine kontinuierliche Beobachtung des Filtrationsverlaufes und die Bestimmung des Filtrationsendes.

Zur Bestimmung des auf die Kuchenhöhe bezogenen Filtrationswiderstandes αH wird der Filtratanfall über die Zeit aufgetragen, wie in Abbildung 2 dargestellt, und nach nachstehender Formel berechnet.[3]

$$\alpha H\,(\Delta p) = b * \frac{A\text{^}2 * \Delta p}{k * \eta} \quad \text{mit} \quad k = A * \frac{He}{Ve}$$

$\alpha_H\, b$	bezogener Filterkuchenwiderstand [1/m²]
Δp	Druckdifferenz während der Filtration [Pa]
A	Filterfläche [m²]
k	Konzentrationskonstante
η	dynamische Viskosität der Flüssigkeit [Pa*s]
He	Kuchenhöhe am Ende der Filtration [m]
Ve	Filtratvolumen am Ende der Filtration [m³]

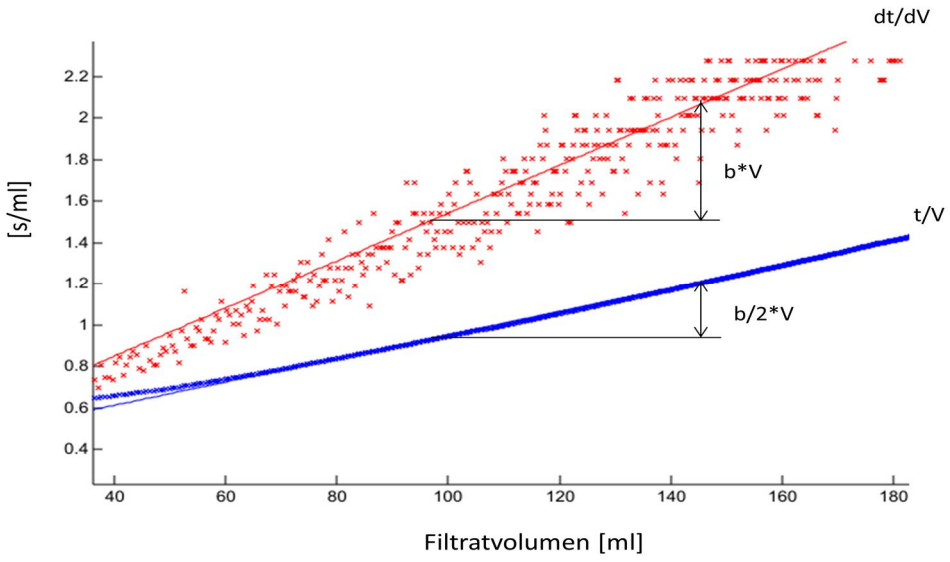

Abbildung 2 Graphische Auswertung des Filtratanfalls über die Zeit am Beispiel von Laktose in Wasser

Um Schwankungen in der Auswertmethodik bezüglich des Startzeitpunktes zu verringern, wird als eindeutiges Startkriterium gleiche Steigung der Regressionsgeraden der differentiellen und der konventionellen Auftragungsmethodik festgelegt. Das En-

de der Filtration ist als Abfallen der differentiell aufgetragenen Kurve definiert.[4] Nach Bedarf muss der Start bzw. der Endpunkt trotzdem von Hand korrigiert werden.

2.5 Auswertung

Bei der Filtration feiner Partikel spielen Partikel-Partikel Wechselwirkungen der DLVO Theorie folgend eine große Rolle [5] und der Einfluss des verwendeten Lösungsmittels ist deutlich erkennbar (siehe Abbildung 3 und 4). Auch bei organischen Partikeln können Schwankungen um mehr als das 30-Fache nachgewiesen werden. Dieser Einfluss nimmt bei größer werdenden Partikeln ab, wie in Abbildung 3 eindeutig feststellbar ist und entspricht somit ebenfalls den bekannten Theorien.[6]

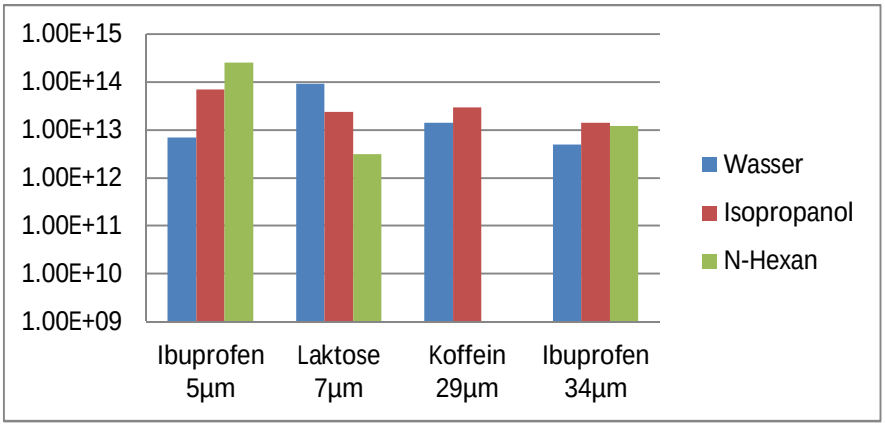

Abbildung 3 bezogener Kuchenwiderstand αH [1/m2] in Abhängigkeit des Lösungsmittelsystems

Die Erhöhung der Filterwiderstände resultiert aus einer dichteren Anordnung der Partikel. Wie bereits für anorganische Partikel festgestellt, ist diese aus veränderten elektrostatischen Wechselwirkungen sowie unterschiedlicher Benetzbarkeit der Feststoffe durch die Lösungsmittel begründet. Hydrophobe Wechselwirkungskräfte spielen ebenfalls eine entscheidende Rolle. Ein Vergleich von Abbildung 3 und 4 zeigt deutlich den Zusammenhang zwischen hohen Kuchenwiderständen verursacht durch kompakte Filterkuchen.

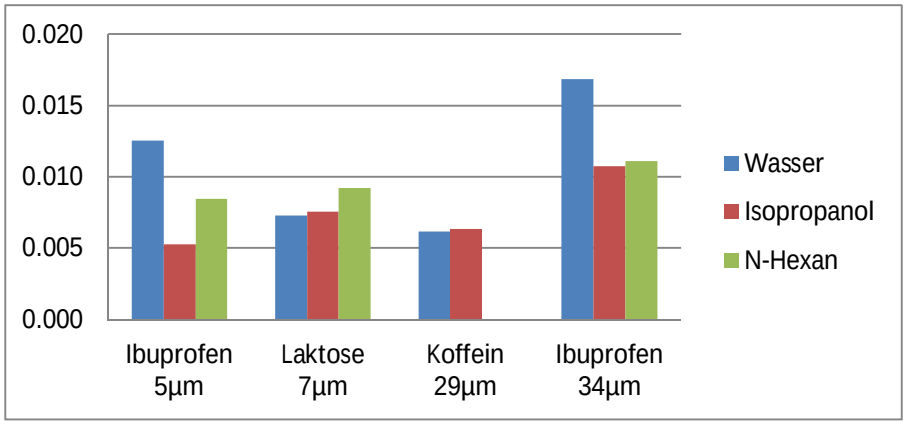

Abbildung 4 Kuchenhöhe [m] in Abhängigkeit des Lösungsmittelsystems

Die verwendeten Lösungsmittel haben also nachweislich einen relevanten Einfluss auf die Kuchenhöhe und somit die Porosität der gebildeten Filterkuchen. Auch im Bezug auf die zu erwartenden Porositäten sind lösungsmittelbedingte Schwankungen für Grobpartikel vergleichsweise geringer.

2.6 Zusammenfassung

Es kann gezeigt werden, dass der Einfluss des Lösungsmittelsystems auf die Filtrationseigenschaften bei organischen Partikeln wesentlich ist. Die hierfür von Peuker und Neubauer angestrebten Überlegungen sind auch für diese Stoffklasse gültig, Differenzen in der Größenordnung der Auswirkung auf Fein- bzw. Grobpartikel sind eindeutig erkennbar. Der Einfluss hydrophober Wechselwirkungen auf die zu erwartenden Filterwiderstände kann vorerst nicht eindeutig quantifiziert werden, obwohl für feine Partikel von Laktose und Ibuprofen eindeutige Tendenzen erkennbar sind.

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3. Continuous Processing of API Suspensions via Dynamic Cross-flow Filtration[4]

3.1 Abstract

Over the last years, continuous manufacturing (CM) has created significant interest in the pharmaceutical industry. Continuous filtration at low flow rates and high solid loadings poses however a significant challenge. A commercially available, continuously operating, dynamic cross flow filtration device (CFF), is tested and characterized. It is shown that the CFF is a highly suitable technology for continuous filtration. For all tested model APIs, a material-specific strictly linear relationship between feed and permeate rate is identified. Moreover, for each tested substance, a constant concentration factor is reached. A one-parameter model based on a linear equation is suitable to fully describe the CFF filtration performance. This rather unexpected finding and the concentration polarization layer buildup is analyzed and a basic model to describe the observed filtration behavior is developed.

[4] This chapter is based on: J.S. Gursch, R. Hohl, G. Toschkoff, D. Dujmovic, J. Brozio, M. Krumme, N. Rasenack, J.G. Khinast"Continuous Processing of API Suspensions via Dynamic Cross-flow Filtration ", Journal of Pharmaceutical Sciences, accepted for publication

3.2 Introduction

Over the last years, continuous manufacturing (CM) has created significant interest in the pharmaceutical industry due to the numerous advantages already demonstrated in other industries. Especially, the flexibility with respect to process development, the higher inherent quality of products and the ability to shorten supply chains are often cited. In this context, demands for novel, continuously-operated production equipment are increasing. While many pharmaceutical manufacturing systems can be easily transformed into continuous processes, such as roller compaction or tableting, other processes pose real challenges. In the field of primary manufacturing, continuous synthesis and separation processes can be implemented based on the vast experience from other industries. For secondary manufacturing, significant efforts have been devoted to the development of continuous processes, such as continuous blending, agglomeration and tableting. However, the interface between primary and secondary manufacturing, i.e., filtration of the crystallization slurry and subsequent drying, is still an open issue, especially at the required small scales

Moreover, flexibility concerning the processed materials is a must as equipment is no longer specifically dedicated to one specific product.[1],[2] In addition, a broad range of material throughput must be achievable, ranging from a kg per hour at the lower end to hundreds of kilos per hour at the high end. While continuous manufacturing technology for higher throughputs is more common, the same cannot be said for “small” products. However, highly-active drugs are on the rise, where a few hundred kilograms constitute a yearly world-wide supply.[3] Thus, small-scale equipment is increasingly important and – in some processes – represents a bottleneck for CM, e.g., in filtration and drying. Clinical batches can be produced on small-scale equipment as well. Scale-up of continuous equipment can be subsequently realized by simply increasing production times.[4]

In this work, we analyze a continuously operating, dynamic cross-flow filtration device (CFF) that is used for solid-liquid separation during downstream manufacturing. The CFF’s very high separation efficiency (low turbidity, etc.) [5] makes this membrane separation technology especially interesting for pharmaceutical manufacturing.

CFF allows separation of particles ranging from 0.01 to 200 µm (micro-filtration, ultra-filtration, dia-filtration).[6] The possibility to increase permeate rates through higher shear rates at the membrane enables efficient treatment of otherwise hard-to-filter suspensions.[7] Thus, high flexibility is given concerning processable feed suspensions. As during dynamic filtration, shear rates are generated by moving parts, decoupling of the membrane shear rate from the inlet flow rate is accomplished.[8] Thus, the requirement for changing throughputs can also be met. To overcome the drawback of the limited membrane area and elevated equipment costs due to the need or moving parts,[8] a large variety of CFF designs is available on the market.

According to the means of shear induction, three basic types are distinguished, i.e., vibrating systems, systems with rotating membrane disks and systems with stirrers near a stationary membrane.[7] Vibrating systems such as the VSEP® by New Logic, USA, or the PallSep® by Pall Corporation, USA, are very energy-efficient and can also process shear-sensitive materials. Rotating disk systems, such as the MSD® by GEA Westfalia Separator Group, Germany, or the Krauss-Maffei DCF® cross-flow filter by Andritz Separation, Germany, use overlapping rotating ceramic discs to induce shear. Another rotating disk system, the Zelix Membrane System® by Pantreon, Austria, consists of disk stacks revolving around a central axis. Systems with stirrers and stationary membranes are, for example, the Dyno® by Bokela GmbH, Germany, or the Optifilter CR® by Metso Paper, Finland.

The CFF analyzed in this study was chosen due to its capacity to handle highly viscous slurries. In vibratory systems, highly viscous slurries can lead to membrane blockage. Intermeshing rotating disks risk wedging and breakage of the ceramic membranes if a certain material-dependent viscosity limit is exceeded. In contrast, CFF systems with stationary membranes promise enhanced capacity to treat highly viscous slurries. Specifically, the Dyno system was selected due to its flexible modular scale-up possibility and availability of a single-chamber lab-scale system, the Dynotest®. Furthermore, the equipment offers the possibility of feeding a washing liquid directly to the filtration chamber. Dilution washing may be achieved easily by adding a static mixer (for washing liquid addition), followed by a second membrane filter. While

such a setup was successfully implemented, we do not address this aspect in this work.

To evaluate the CFF performance under representative conditions, two crystalline material systems were chosen relevant for the pharmaceutical industry (Ibuprofen in water, lactose in water) thereby also account for the strong influence of the model particles on filtration performance.[9]–[12] The first one is sparingly soluble, the second one highly soluble in water.

The scope of this paper comprises an overview of the experimental results, including an analysis of filtration behavior over time, e.g. filtration pressure, permeate flow, and retentate concentration. The main focus is the development of a fundamental theoretical model allowing and understanding of the experimental results.

3.3 Materials and Methods

3.3.1 Filtration Equipment

A Dynotest® system (Bokela GmbH, Germany) was used as filtration equipment. The unit is equipped with a 0.55 kW/400 V motor to drive a directly coupled rotor in line of the axis of the filter disk. The cooled process chamber can be opened for cleaning and changing the membrane as depicted in Figure 1. The filtration area is 130 cm^2. The maximum filtration pressure is 7 bar, absolute.

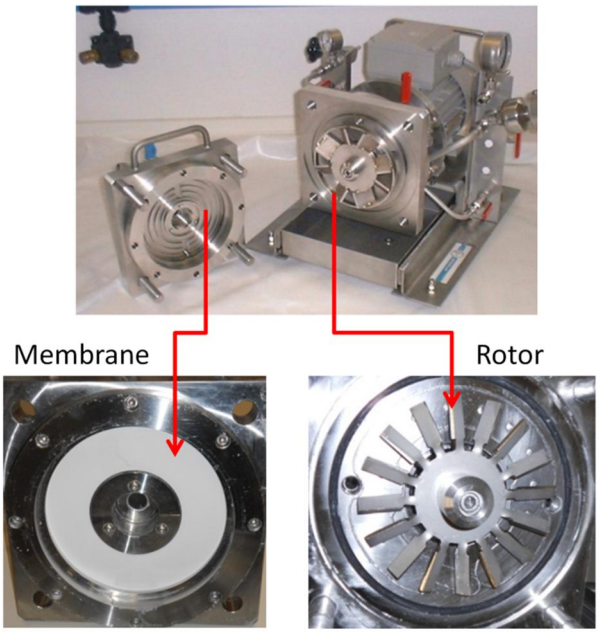

Figure 1 Pictures of the CFF (Dynotest® by Bokela GmbH) with rotor and ceramic membrane

A peristaltic pump type MX10S-10/20® (Knoll Maschinenbau GmbH, Germany) was used to feed material into the process chamber. Feed throughput was measured using an electromagnetic flow meter type FSM4000® (ABB GmbH) with ≤0.5% accuracy. Permeate throughput was measured using an electromagnetic flow meter type 008AP001E® (Honsberg Instruments GmbH, Germany) with 2.5% accuracy. To measure filtration pressure, a pressure sensor type 261GS® (ABB GmbH) with ±0.1% accuracy was implemented. A simplified P&I schema is depicted in Figure 2.

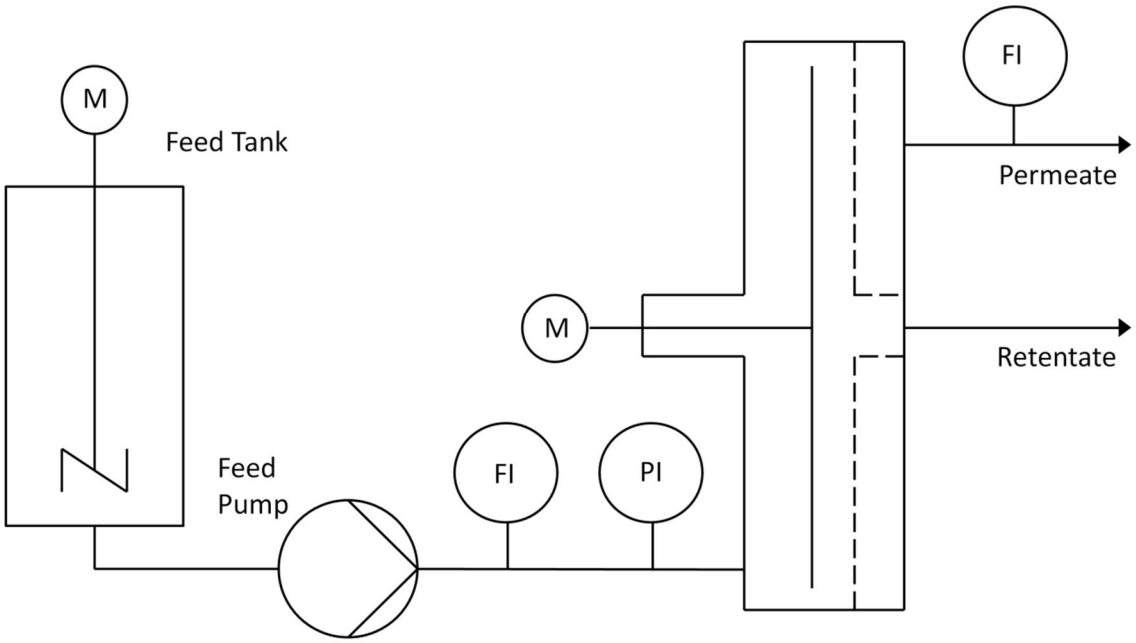

Figure 2 Schematic filtration setup

3.3.2 Materials

Alpha-lactose monohydrate (Granulac_230® donated by Meggle AG, Austria) with a volume mean particle size of 19 µm, was dispersed in water. To prevent changes of particle size or shape due to dissolution, water saturated with pre-dissolved lactose (180g/l) was used. Ibuprofen_25 with the volume mean particle size of 32 µm (BASF Switzerland) was also dispersed in water. In the case of Ibuprofen, 8 g sodium pyrophosphate tetrabasic (SPT) provided by Sigma-Aldrich were pre-dissolved in each liter of water to ensure uniform dispersion. Solubility effects of Ibuprofen in water are negligible.

The membranes were aluminum oxide disks with mean pore size of 0.5 µm, inner diameter of 65 mm, outer diameter of 156 mm and thickness of 2 mm (Kerafol Keramische Folien GmbH, Germany). For validation experiments, some membranes had to be partially blocked. For this, a thin layer of acrylic liquor 0330® by Zeus GmbH, Germany, was brushed onto the membrane.

3.3.3 Material Characterization

Raw materials and products were thoroughly characterized. Q3 particle size distribution (PSD), shown in Figure 3, was determined using laser diffraction via Helos® (Sympatec GmbH, Germany, dry dispersing unit Rhodos®) equipped with the Sympatec Software, WINDOX 5.6.0.0®. The dispersion pressure was 1.5 bar.

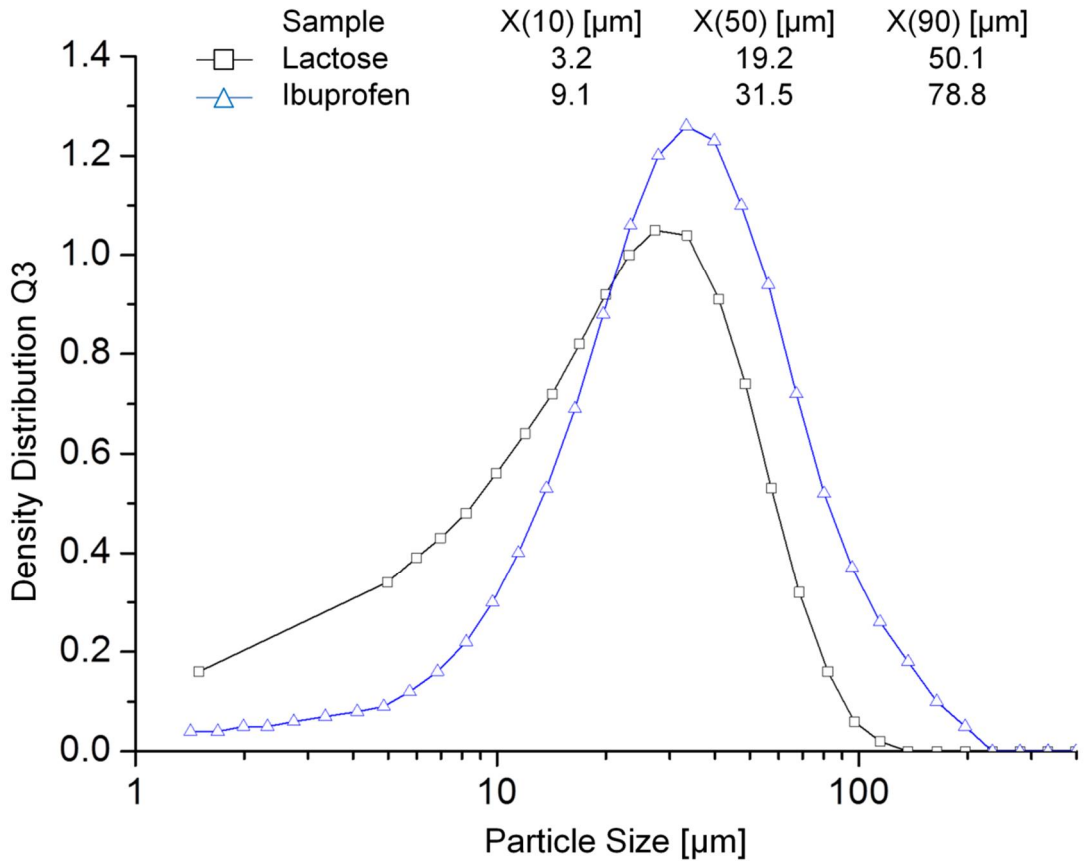

Figure 3 PSD of raw materials

Particle surface and shape were examined with a scanning electron microscope (SEM) (VEGA 3 SEM, TESCAN, Czech Republic) operating at 10-20kV. Images of the particles are shown in Figure 4. The samples were gold-sputtered (Sputter Coater 108auto, Cressington, England). Lactose particles were more of cuboid shape with fines attached to the surface, while ibuprofen particles had an elongated shape (short of being needles) with very smooth surfaces.

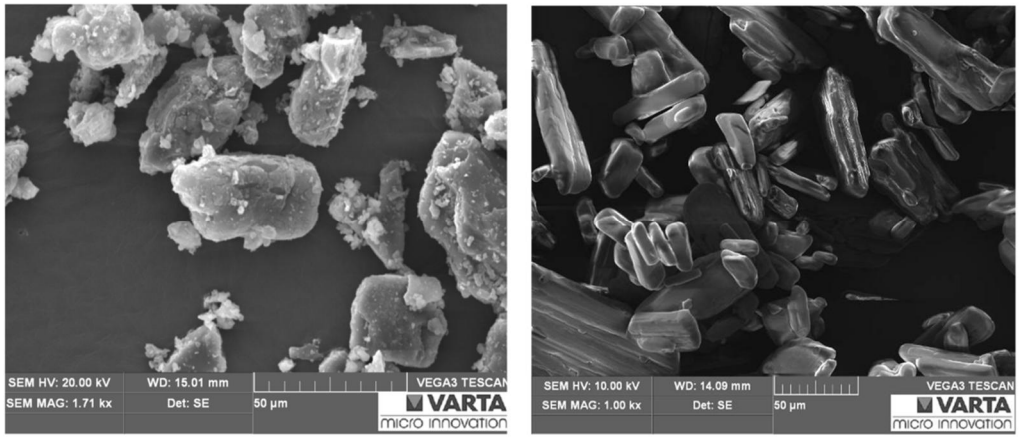

Figure 4 SEM images of lactose (left) and Ibuprofen (right)

Suspension viscosity was measured using a rotational rheometer (MCR 300, Anton Paar, Austria) with a double gap measuring system (DG26.7-TI/ TEZ 150P, Anton Paar, Austria). Viscosity data of lactose suspensions are shown in Figure 5.

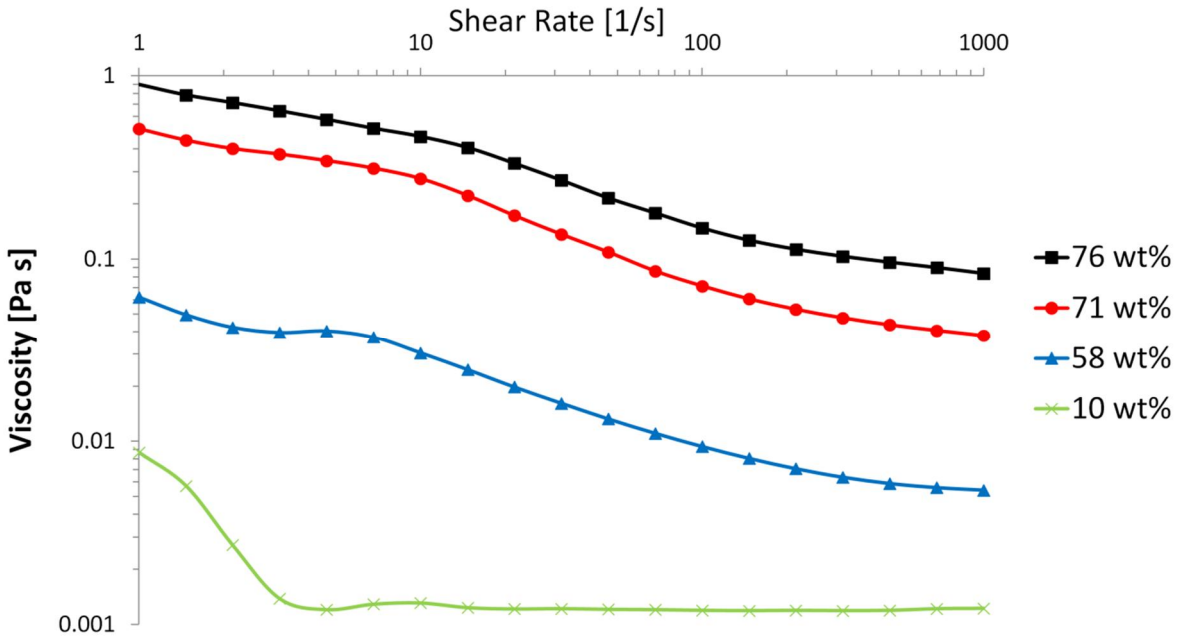

Figure 5 Viscosity over shear rate for lactose suspensions in double logarithmic scale

The viscosity for Ibuprofen suspensions is presented in Figure 6. Both suspensions showed shear thinning behaviour. Rotational viscosity increased with increasing solid content.

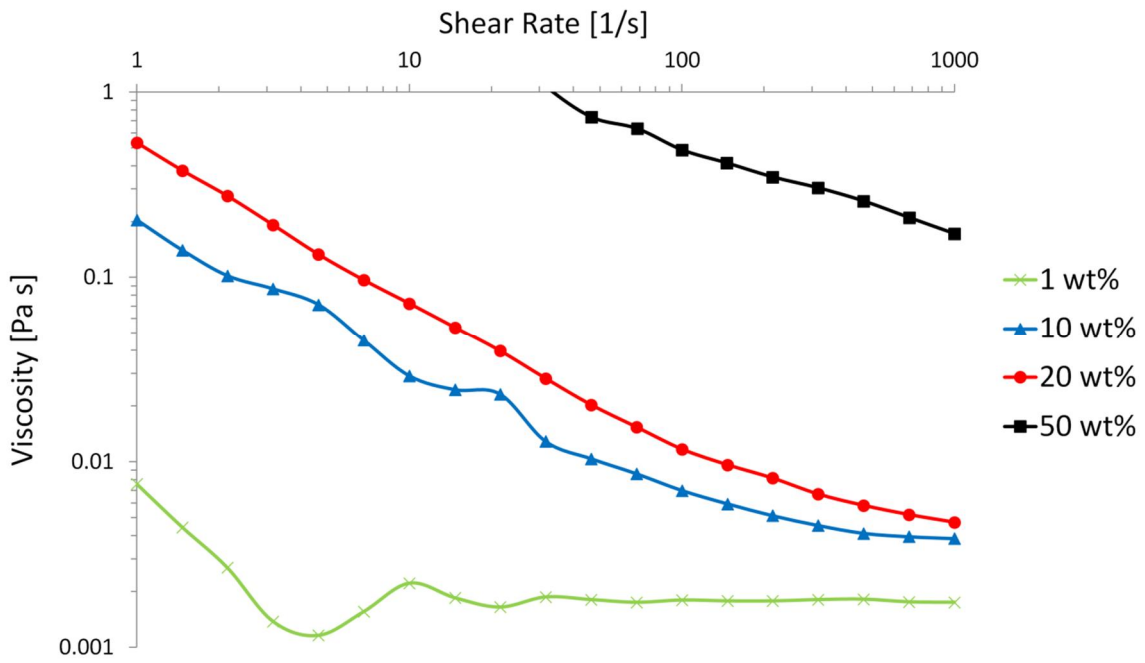

Figure 6 Viscosity over shear rate for Ibuprofen suspensions in double logarithmic scale

Residual moisture was analyzed using a thermo-gravimetric method (MLS_N Version 2.0, Kern & Sohn GmbH, Germany). The drying temperatures for the lactose and Ibuprofen-SPT mixtures were kept constant at 105 °C and 65 °C, respectively. The final residual moisture content was determined after 240 s of weight consistency smaller than 1 mg, which corresponds to approximately 0.05‰ relative weight change. The concentration values indicated refer to wet basis.

3.3.4 Methods

All membranes were wetted in water for an hour prior to use to avoid partial blockage of the membrane by air enclosed in the internal membrane structure. After assembly, the CFF was vented and for an hour rinsed with water, to ensure evacuation of all contained air. During this time, the outlet vent was opened and the continuous operation mode was started. Subsequently, the feed was switched from water to suspension. The suspension was prepared in a continuously stirred tank and fed to the CFF via a progressive cavity pump. Once a constant permeate flow was obtained, filtration was continued for another hour.

A set of different suspension throughputs and suspension concentrations was tested for each substance, as listed in Table 1. Rotor speed was set to 1400 rpm, indicating the maximum rotation speed to ensure the most efficient disturbance of the concentration polarization layer (CPL), i.e., to ensure the highest permeate rates and, therefore, the highest retentate solid concentrations.

Table 1 Tested parameter range

Substance	Feed flow [l/h]	Feed solid concentration [wt%]
Lactose	4	1;10;30
	10	45
	36	1;30
Ibuprofen	4	1;5;10;20;30
	8	1;30
	10	10
	36	1;30

The residual moisture of the steady-state product was calculated from the feed and permeate flow measurements. Additionally, retentate samples were taken and dried in a thermo-gravimetric balance. The concentration factor (CF) was calculated according to [13] as the ratio of retentate and feed concentration, respectively.

$$CF = \frac{retentate\ solid\ concentration}{feed\ solid\ concentration} \qquad \textit{Equation 1}$$

Computational fluid dynamics (CFD) simulations were conducted using the software package AVL Fire and a 2.5 Mio hexahedron mesh. Momentum, continuum and energy equations were solved. The k-zeta-f turbulence model was used. As boundary conditions an inlet mass flow was given and constant atmospheric pressure was assumed at the outlet. To model the rotor rotation the multi reference frame (MRF) approach was applied.

3.4 Results and Discussion

In all experiments, a material-dependent linear relationship of the permeate flow as a function cumulated feed flow was found as indicated in Figure 7. For reasons of clarity, only two extreme cases are shown for each substance. Within the varied parameter range filtration on the CFF resulted in an almost constant concentration factor. That is, after a start-up period (<3600s), a material-dependent concentration factor exists, independently of the feed rate or feed concentration. Thus, a linear equation of the following form can be used to describe the input-output relation and the concentration factor can be expressed as a function of the proportionality constant k:

$$permeate\,rate = k \cdot feed\,rate \qquad \textit{Equation 2}$$

$$CF = \frac{\frac{solid\,feed\,rate}{(1-k)\cdot feed\,rate}}{\frac{solid\,feed\,rate}{feed\,rate}} = \frac{1}{1-k} \qquad \textit{Equation 3}$$

CF was material-dependent, but otherwise constant for the tested parameter range.

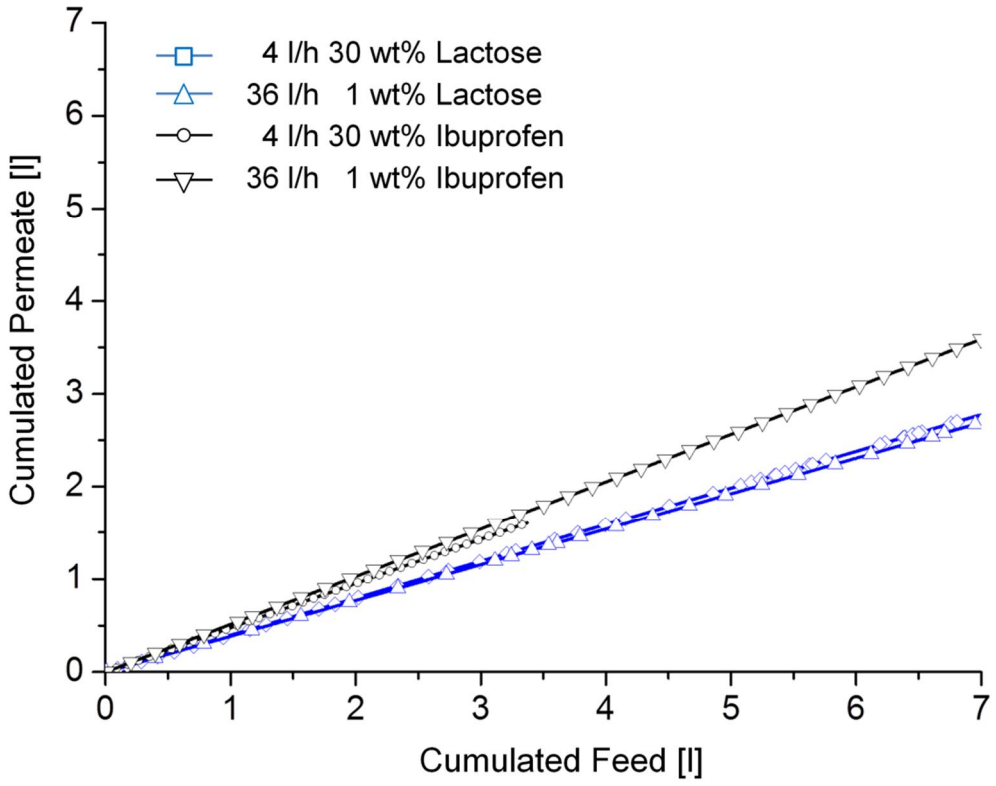

Figure 7 Cumulative permeate flow over cumulative feed flow. The gradients for all runs, as listed in Table 1, show a constant material-dependent slope. For reasons of clarity, only two extreme cases are shown for each model substance (only every 80th data point plotted)

During all runs, trans-membrane pressure reached a constant level of 0.41 bar after the start-up phase, as indicated in Figure 8,with centrifugal forces caused by the rotor constituting a large part of the measured pressure level.

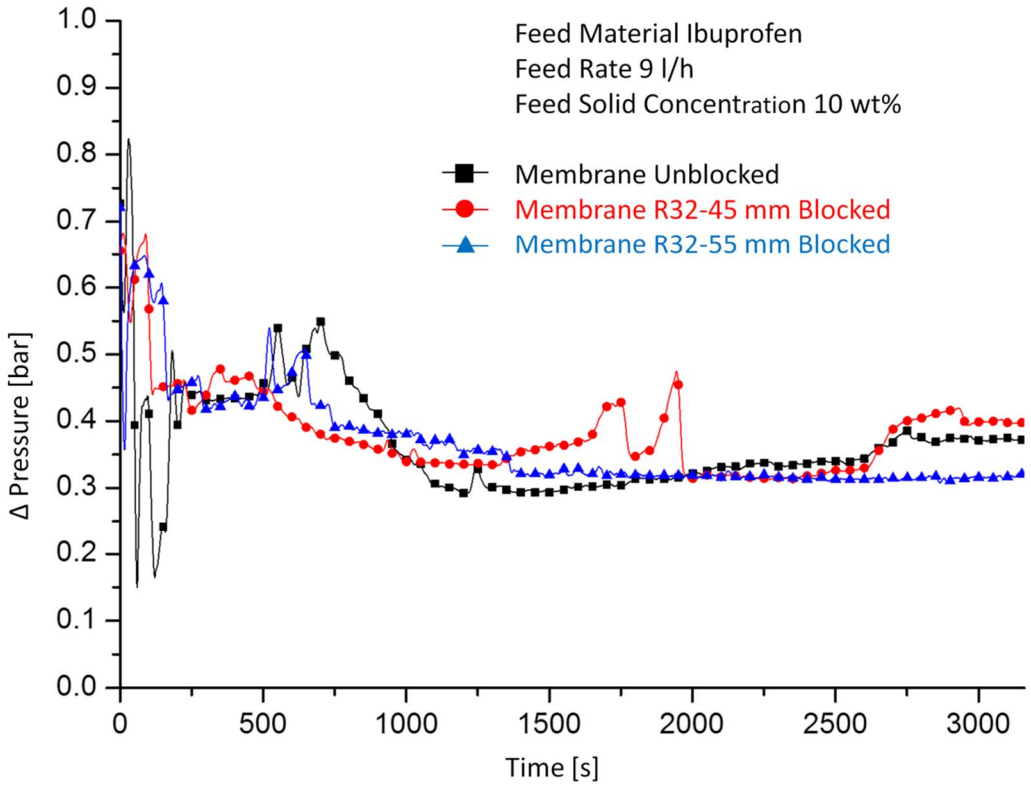

Figure 8. Pressure difference for partially blocked and unblocked membranes (only every 50th data point plotted). The typical transmembrane pressure difference of 0.41 bar was not reached for the rigorously blocked membrane (R32-55 mm). A slight variation in transmembrane pressure difference (0.025 bar) can be observed between the unblocked and the R32-45 mm blocked membrane. However, as all experiments were conducted with different membranes, slight variations due to variability of membrane resistance are to be expected

The maximum feed solid concentration was 30 wt% for Ibuprofen and 45 wt% for lactose. With a CF of 2 for Ibuprofen and 1.7 for lactose this equals a final retentate solid concentration of 60 wt% for Ibuprofen and 76 wt% for lactose. For higher solid concentrations, rotor blockage occurred and the process deteriorated.

In dynamic cross-flow filtration, a concentration polarization layer (CPL) or a cake layer is established throughout the process. Formation of this layer in combination with the filter medium resistance is a limiting factor for filtration performance. The higher the CPL resistance is, the lower the achievable permeate flow becomes. Process parameters influencing CPL resistance are the particle concentration, the rotor

speed and the transmembrane pressure.[14] Transmembrane pressure and rotor speed were constant throughout our experiments. Particle concentration, however, varied strongly. Bouzerar et al. showed in a similar cross-flow device, that increasing suspension concentrations leads to a strong increase of filtration resistance, and in consequence, to a decrease of permeate flow.[15] A strictly constant concentration factor, as shown in Figure 9, leading to a permeate flow independent of the feed solid concentration was unexpected. Especially so, as the relation also holds for highly concentrated feed slurries with solid concentration of, e.g. for Ibuprofen, 30 wt% and a corresponding retentate solid concentration of 60 wt%. As the observed effect is dependent on the CPL layer buildup, an extrapolation to 0 wt% is not valid. A minimum of material needs to be present.

3.4.1 Relevance for CPL Estimation

In classical filtration theory, Darcy's equation can be used to calculate the permeate flux (J) as a function of transmembrane pressure (Δp), dynamic viscosity of the permeate (η), membrane resistance (R_m) and CPL or cake layer resistance (R_C).[16]

$$J(t) = \frac{\Delta p}{\eta * (R_m + R_C)} \qquad \textit{Equation 4}$$

As shown in Figure 9, permeate flow was independent of the tested solid concentration range.

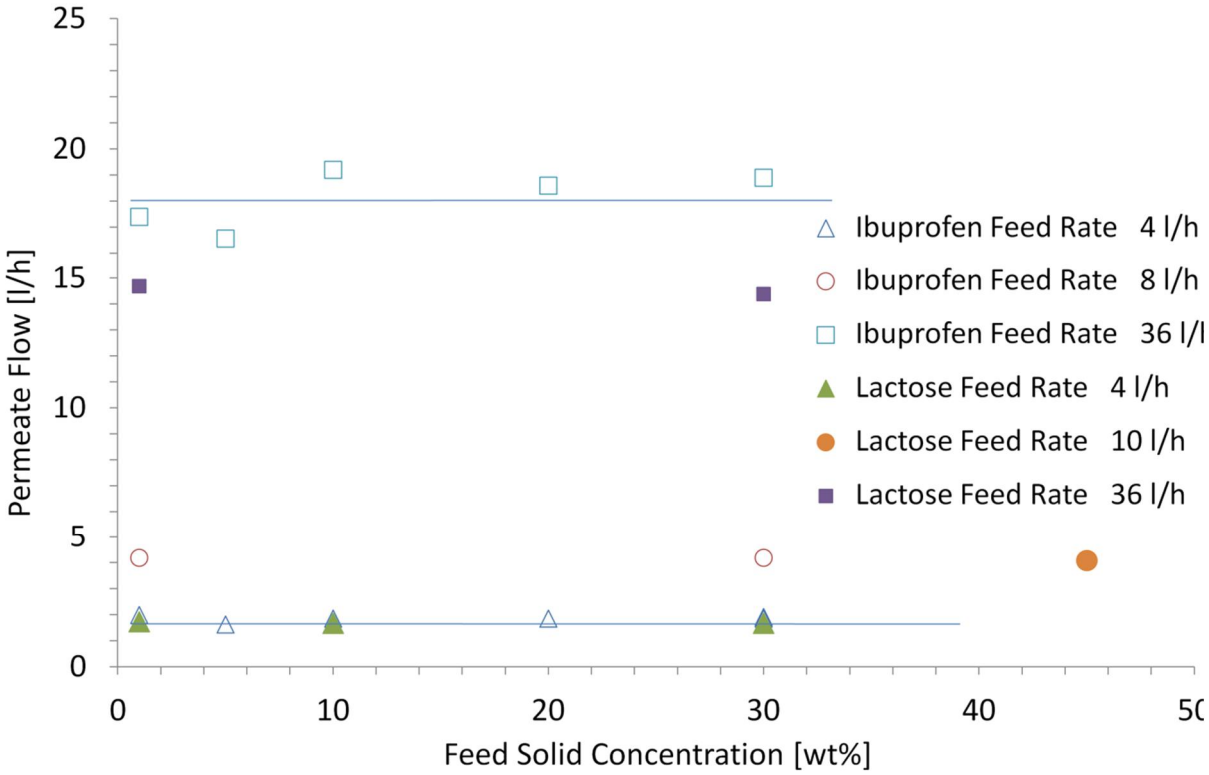

Figure 9 Permeate flow over feed solid concentration for lactose and Ibuprofen

This becomes apparent when comparing (for example) all runs carried out with Ibuprofen and a feed rate of 8 l/h. In all cases, a constant permeate flow of 4 l/h was reached. According to Darcy's law, no variation in the permeate flow implies that CPL resistance stayed constant for all runs with identical feed rate. Independently of feed solid concentration and feed rate, a constant CF of two was reached, that is, in all cases, the initial solid concentration could be doubled. As shown in Figure 7, all experiments can be described via linear Equation 2 using a material-dependent k. It is apparent that high feed rates induce high permeate rates. That is, the permeate rate varies with the feed rate. According to Eq. 4, a variation of the permeate rate is only possible via a variation in CPL resistance, as all other factors are constant. Therefore, it can be concluded that CPL resistance varies with feed rate but not with the feed concentration.

3.4.2 CPL Model

Three possible mechanisms can account for variations of CPL resistance: variations of CPL thickness, variation of the CPL-covered area or variations of CPL internal properties. These three possibilities are discussed and analyzed in the following paragraphs:

(1) CPL thickness varies

The possibility is that CPL or cake layer thickness varies with feed rate. That is, higher permeate rates lead to a reduction of CPL thickness, with the free membrane area remaining unchanged, as depicted in Figure 10. The actual CPL shape might deviate from this simplified depiction, due to a shear rate gradient alongside the radial direction, as also indicated in Figure 11.

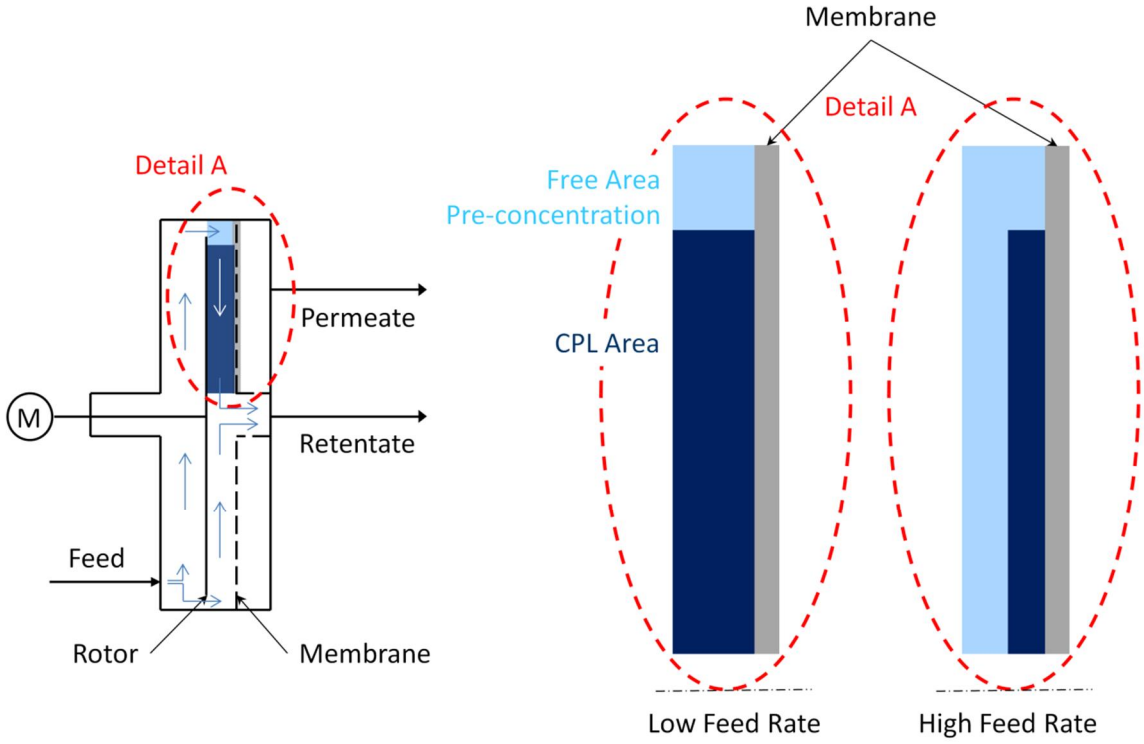

Figure 10 Schematic of the filter system and of a possible CPL structure suggesting a variation of CPL thickness in dependence of the feed rate. The axis of rotation is shown as dashed line. Suspension flow occurs from the outside towards the inside over the membrane as shown. The assumption is that a certain region outside (due to high velocity of the rotor) is free of a CPL

In general, the CPL thickness depends on a set of properties such as pressure, membrane, feed suspension and shear rate. During our experiments, only the feed suspension (i.e., via

feed concentration) and the shear rate (i.e., via feed rate) were changed. With the feed concentration having no apparent influence on separation performance, the only influencing parameter remaining is the feed rate. Thus, the feed flow rate would have to change the shear layer in the process chamber significantly enough to influence the CPL layer thickness.

To verify this hypothesis, CFD simulations were conducted. The CFD setup was strongly simplified, as no particles were considered. Viscosity was set to a fix value of 0.263 Pas (higher viscosity values would only lead to reduced shear rates at the membrane). The feed flow rate was set to 12 l/h for one case and 52 l/h for the other. In both cases rotor speed was set to 1400 rpm. Flow through the membrane was not simulated. Despite these strong simplifications, valuable process insight could be generated.

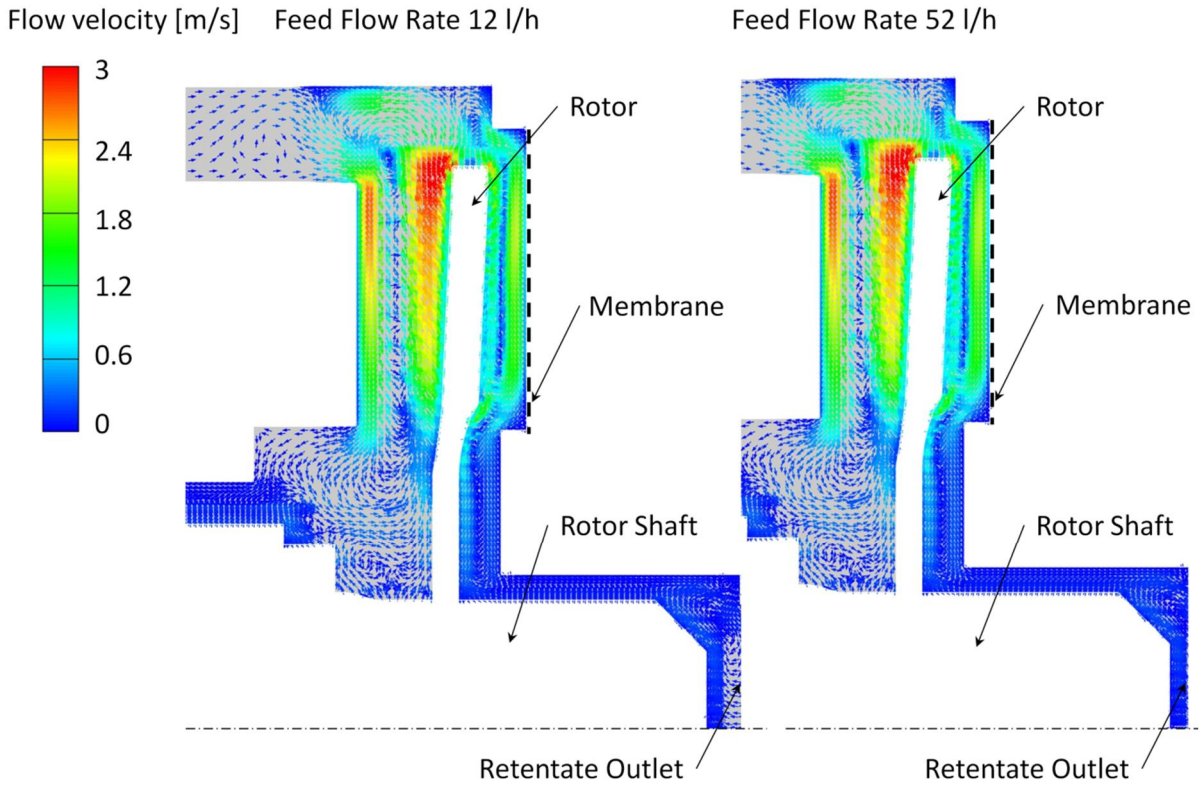

Figure 11 Influence of the feed flow rate on the velocity profile in the CFF. The axis of rotation is shown as dashed line

As shown in Figure 11, the strong impact of the CFF rotors on the flow field marginalizes all possible influences of the feed rate on the flow field in the process chamber.

Therefore, feed rate-induced shear rate changes significant enough to influence CPL thickness seem unrealistic.

(2) CPL radial extension varies

As mentioned above, we assume that due to higher shear forces towards the outer part of the rotor, the CPL layer is thin outside and will develop towards the inner radius. Thus, most of the liquid will be filtered in the outer membrane region. In consequence, the more concentrated slurry builds a CPL or a cake layer closer to the inner membrane region, before being eluted from the process chamber. The CFD data, as shown in Figure 11, show no apparent change of flow structure over the whole range of tested flow rates. However, viscosity changes due to the buildup of a CPL layer and for different solids loadings were not accounted for in the simulations. Thus, variations of the CPL-covered area or variations of the CPL internal properties are not accounted for by the CFD simulation. The second hypothesis to explain the linear relation in Eq. 2 assumes that the CPL covered area varies (or more precisely that the thickness and structure of the CPL changes as function of the feed rates). That is, higher permeate rates lead to a reduction of the CPL-covered membrane area, as illustrated in Figure 12. This implicates that for small feed rates only a small portion of the membrane is used as functional area. Put differently, a small portion of the membrane might suffice to separate a small volume of the liquid phase. The remaining membrane area will be covered by a CPL layer. The actual CPL shape might deviate from the simplified depiction, due to a shear rate gradient alongside the radial direction, as also indicated in Figure 11.

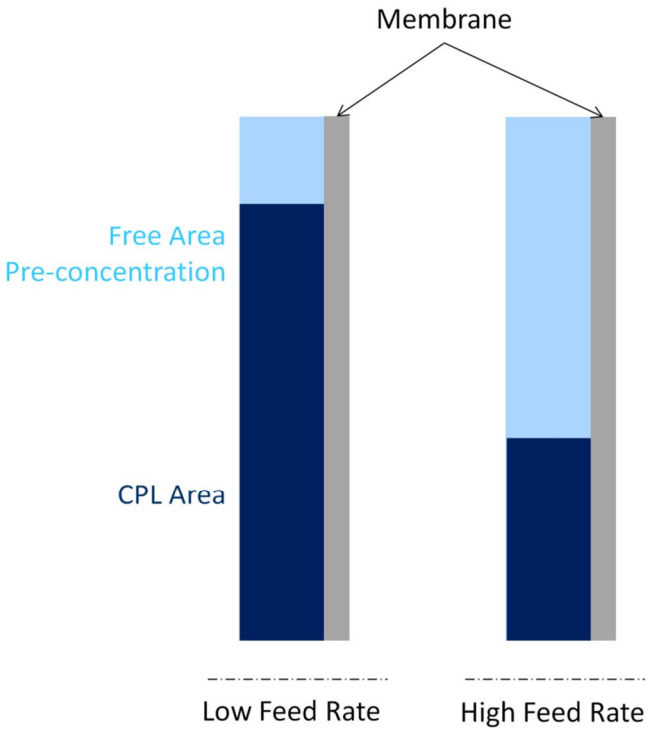

Figure 12 Schematic of the underlying effects concerning CPL buildup

To further evaluate this hypothesis, a membrane was prepared with the inner membrane area being blocked with an acrylic lacquer (blocked area between radius 32-45 mm) as shown in Figure 13. Due to the absence of flow through the membrane in the blocked area, a CPL cannot build up. Nonetheless, filtration performance should remain unchanged, given that the blocked area was “unused” and did not participate in the filtration.

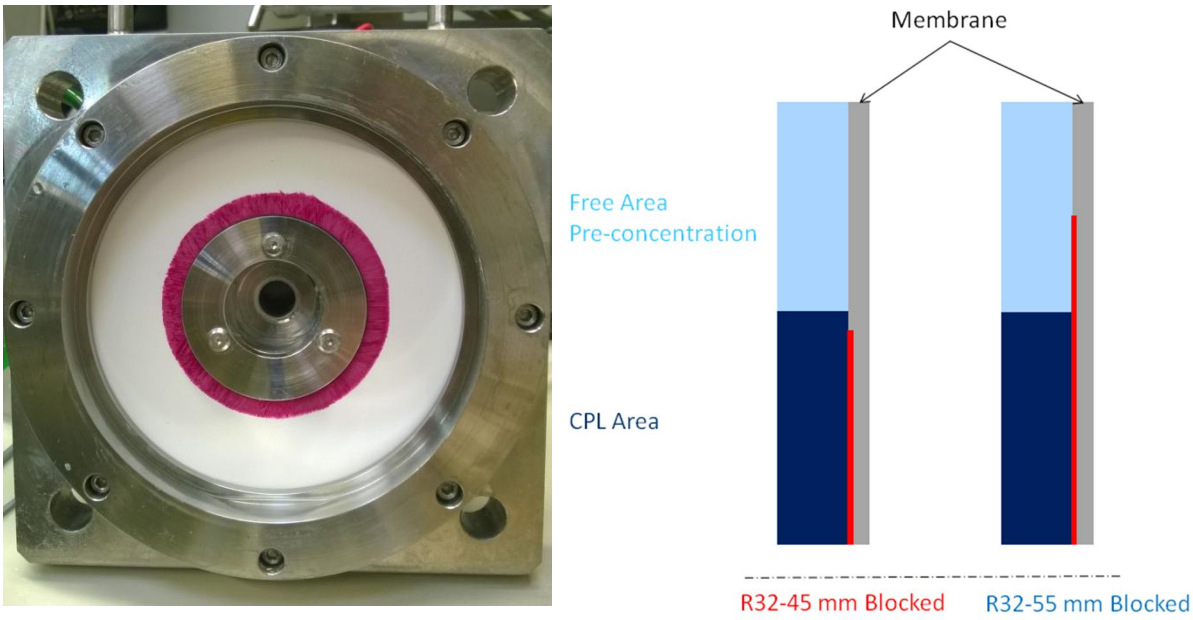

Figure 13 Partially blocked membrane used during verification runs and schematic of the CPL buildup in correspondence to blocked membrane area. With a blocked membrane, actual CPL buildup might not occur as indicated due to the absence of flow through the blocked membrane area

After a start-up phase, the permeate flow of the artificially blocked membrane (R32-45 mm) and the unblocked membrane reach the same constant level as shown in Figure 14. Even though 24% of the membrane area were nonfunctional, filtration performance did not change. According to the previously developed theory, this indicates that only a certain portion of the membrane area is used during filtration of low feed throughputs. However, blockage of the membrane area between R32-55 mm (48% of membrane area) led to strong reduction of the permeate stream. Furthermore the typical transmembrane pressure difference of 0.41 bar was not reached, as shown in Figure 8.

According to our hypothesis, the same feed-permeate ratio could have been achieved using the rigorously blocked membrane (blockage between R32-55 mm; 48% of membrane area) for a feed rate below 9 l/h. In contrast, a feed rate increase beyond a critical level would cause a deviation from the otherwise constant feed-permeate ratio when using the 24% blocked membrane. However determination of exact threshold values is not the focus of this study.

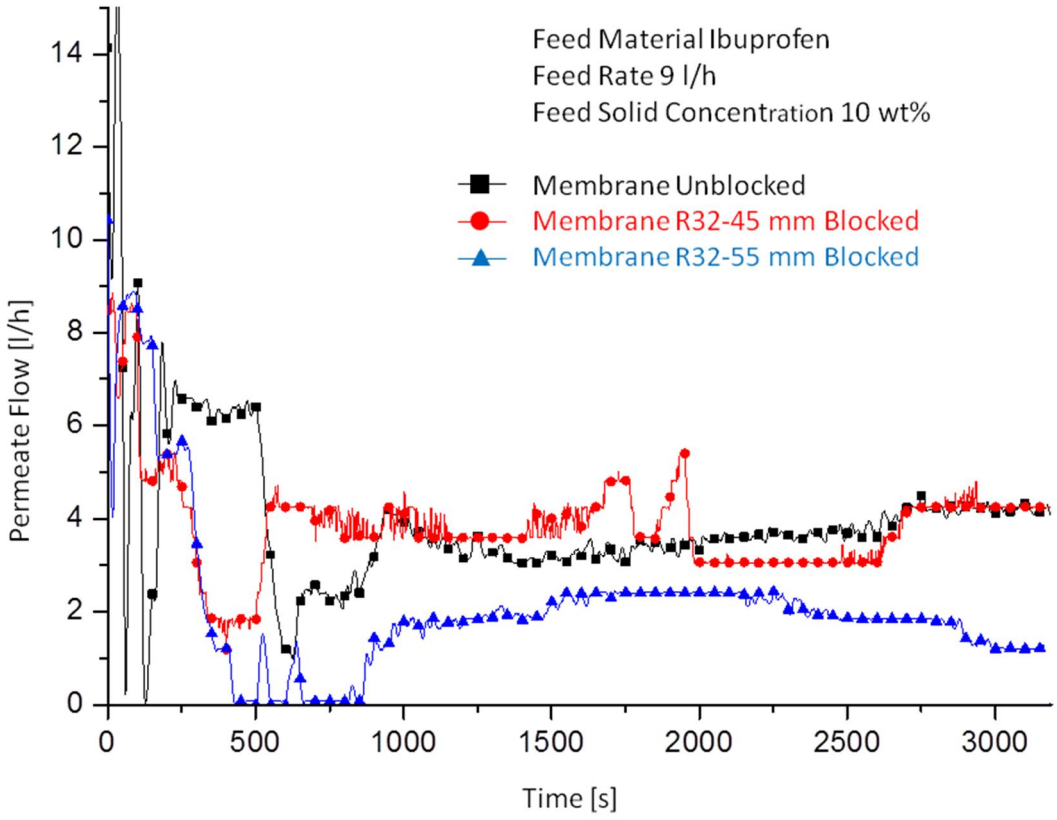

Figure 14 Permeate flow rate for partially blocked and unblocked membranes (only every 50th data point plotted)

With these experiments it could be shown that there is a significant difference in filtration performance alongside the radius of the membrane. With filtration pressure being at a constant level during all runs, the difference of filtration performance must be caused by differences in CPL layer buildup alongside the radius of the membrane. The possibility of a combined effect with variations in the CPL's internal properties (hypotheses 3) depending on the feed rate remains. However, a highly complex experimental setup would be required to directly measure form and structure of the CPL geometry, without disturbing the flow. Furthermore, the developed theory of radial changes in the CPL-covered area, explains well the encountered filtration behavior. The observed strictly-linear relationship between the feed and permeate rates could be confirmed for unblocked membranes over the whole range of setup-specific, achievable feed rates (4 to 36 l/h). Deviations of the linear relationship are to be ex-

pected for feed rates well above the tested feed range, that is, if the required functional area exceeds the available membrane area.

3.5 Conclusion

In this study a membrane filtration system was investigated with respect to its applicability to the continuous filtration of an API slurry with a low flow rate and rather small crystals down to 1 µm. A wide range of feed rates and feed concentrations were evaluated to assure the flexibility and agility of the system under investigation. For all tested substances, a material-specific, strictly-linear relationship between the feed and the permeate rate was identified. For each tested substance, a constant concentration factor was reached. The linear relationship and the constant CF make it very easy to predict filtration performance for any given stream coming from upstream production (i.e., continuous crystallization): only one test has to be conducted (ideally) with an arbitrary feed rate and feed solid concentration to determine the CF value. Once the material-specific CF value is known, the developed one-parameter model suffices to describe the filtration process.

A hypothesis was developed and tested to explain how the CFF filtration behavior is achieved. The investigation established an understanding of CPL or cake layer formation and is suitable to explain the observed filtration behavior. The theory will also be useful for explaining the process behavior when the system is exposed to changing inlet conditions, e.g., fluctuations in the feed rate. Further studies are planned to determine the limit of the linear feed-permeate relation. Here, feed rates of 36 l/h were set as the upper limit, due to the equipment's use as small-scale production equipment.

Maximum final solid concentrations were very high (60 wt% for Ibuprofen and 76 wt% for lactose). In comparison, the achievable solid concentration for the same substances using a batch filtration setup with 3bar pressure difference according to VDI 2762 [10] and as reported in [17] was between 84-90 wt%. For most drug products these final residual moisture levels would be too high (even for batch filtration moisture levels), requiring a subsequent continuous drying step. Nevertheless, effi-

cient mechanical removal of solvent prior to thermal drying is advantageous to keep energy consumption low and to minimize drying time and associated impact on API crystals.[18][19] This also holds true when high-priced solvents have to be recovered after drying. Using a mechanical solid-liquid separation step prior to thermal drying helps to avoid complicated extraction steps.

Thus, the tested CFF is a suitable device to pre-concentrate slurries in a continuous manufacturing process. The low throughput range renders the CFF the most favorable choice for continuous production. Furthermore, its closed-chamber design allows for treatment of toxic solvents and APIs which is a must in pharmaceutical production.

3.6 Acknowledgements

We acknowledge the support of Manuel Zettl, Mario Unterreiter, Arlin Gruber, Markus Gamsriegler, and Daniel Kaiser. Furthermore, we want to thank Bokela GmbH for their support and Meggle AG for donating lactose. We also thank Novartis Pharma AG Basel and Hosokawa Micron B.V. Doetinchem for the financial support.

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4. Dynamic Cross-Flow Filtration: Enhanced Continuous Small-Scale Solid-Liquid Separation [5]

4.1 Abstract

In our previous study, a small-scale dynamic filtration device (SFD) was analyzed and the basic mechanisms governing the filtration process were characterized. The present work aims at improving the device's performance in terms of actual production. An operation mode was developed to increase permeate flow and concentration factors while maintaining a fully continuous production mode. Furthermore, the new operation strategy enables producers to adequately react to the fluctuating feed conditions that may occur due to instabilities in upstream manufacturing steps. As a result, not only filtration performance in terms of permeate rate but also process flexibility can be significantly increased.

[5] This chapter is based on: J.S. Gursch, R. Hohl, D. Dujmovic, J. Brozio, M. Krumme, N. Rasenack, J.G. Khinast "Dynamic Cross-Flow Filtration: Enhanced Continuous Small-Scale Solid-Liquid Separation", internal revision, submitted December 2014

4.2 Introduction

While there is a wide variety of technologies available for high-volume throughputs (e.g., drum pressure filters, belt filters, decanters, and so on), for continuous small-throughput filtration only a few systems are readily available. Meanwhile, the demand for such equipment is increasing. For example, in the pharmaceutical industry continuous production of small-quantity products is on the rise due to the trend towards continuous manufacturing and highly specialized patient-centered drugs.[1] Although some ready-to-use continuous equipment is available, the achievable final solid concentrations are often rather low (i.e., 20 vol.% [2]), rendering the process of solid-liquid separation inefficient.

In our previous study,[3] we reported the use of a commercially available dynamic cross-flow device and demonstrated that it is suitable for producing highly concentrated slurries in a continuous operation mode. While industrial sectors, such as the food and chemical industries have long established continuous manufacturing lines, the pharmaceutical sector has only recently begun to adopt continuous manufacturing (CM) methods.[4] One of the advantages of CM is that time-consuming scale-up can often be avoided. By simply increasing the process time, the same equipment can be used both during the development phases and in the final production,[5] enabling a faster product development and a shorter time-to-market for new drugs.[6] Together with real-time release testing and model-based control strategies, products of consistently high quality can be produced in less time. This way, rejection of large batches can be avoided, resulting in a substantial decrease in quality-associated costs and in the length of the supply chain. [6]–[9]

In our previous study,[3] dynamic cross-flow filtration was shown to be suitable for continuous operation of small throughputs, even at high initial solids concentrations. However, the tested setup had one major restriction: a constant (material-depending) concentration factor (CF) that could not be changed by modifying process conditions (e.g., for Ibuprofen a CF = 2 was obtained). The concentration factor is defined as:

$$CF = \frac{product\ solid\ concentration}{feed\ solid\ concentration} \qquad \textit{Equation 5}$$

Thus, concentration of a feed with low solids loading takes several consecutive steps. For instance, with a concentration of 1 wt% six subsequent steps need to be carried out to concentrate the suspension up to 64 wt%, with each step requiring a complete set of supporting equipment, such as process analytical tools (PAT), pumps, etc. This results in high investment costs and creates additional complexity associated with developing a control strategy for multiple independent process steps.

Therefore, strategies for improving the process effectiveness have to be developed, i.e., by increasing the achievable permeate flow rates and the concentration factors. Various approaches can be identified taking into account Darcy's equation. According to classical filtration theory, the permeate flux (J) can be calculated as a function of transmembrane pressure (Δp), dynamic viscosity (η), membrane resistance (R_m) and concentration polarization layer (CPL) or cake layer resistance (R_C) [10]:

$$J(t) = \frac{\Delta p}{\eta * (R_m + R_C)} \qquad \textit{Equation 6}$$

The following strategies can be considered:

(*1) Reduction of CPL or cake layer resistance:* In many cross-flow applications, the filtered material itself forms a limiting barrier to the flow of liquid through the membrane. In dynamic cross-flow filtration, the limiting barrier is reduced or completely eliminated by shear that is generated either by the material flow itself or the moving parts, e.g., disks or propellers. An increase in the shear rate leads thus to a decrease in layer thickness and an increase in the permeate flow rate.[11]–[14]

(2) Change of filter medium: Sub-optimal filter media can create substantial problems due to filter blockage. Choosing filter media suitable for a specific filtration task (e.g., particle size, solvent polarity, etc.) significantly improves permeate flow rates if membrane resistance represents the rate-limiting step.

(3) Increase in filtration pressure: An increase in the pressure difference as the main driving force in cross-flow filtration leads to an increase in the permeate flow

rates, as long as other effects (e.g., flow reduction due to compaction of the filter cake) can be avoided.

As shear rates were already set to maximal levels (option one) and optimal filter media were already chosen (option two) during our previous study [3] only option three, increase of filtration pressure remains to be addressed.

The tested dynamic cross-flow equipment can alternately open and close the retentate (i.e., the highly concentrated slurry outlet) exit, leading to a pulsating flow at the outlet. During the closed time period, the chamber pressure rises and higher permeate flow rates can be achieved. This oscillating, quasi-continuous operation mode can also be implemented in the equipment manufacturer's larger filtration devices and is already successfully used in industrial applications.

In the fully continuous operation mode, the filtration pressure was constant throughout all tested ranges of feed solid concentration and feed rates.[3] The observed constant pressure level (1.41 bar) results from the nature of free material flow through the equipment in the open continuous mode and a very low flow resistance of the tested equipment itself. Increasing the resistance of flow through the device, e.g., by adding a constriction at the retentate exit, increases the filtration pressure. However, constrictions may cause blockage of the retentate exit at higher concentrations and thus, are not technically relevant.

Another method of increasing the pressure is to establish a pressurized zone at the retentate exit. However, a continuous discharge of the retentate from a pressurized zone has to be established. Such locks are difficult to engineer and are error-prone.

As a final alternative, the driving pressure difference can be enhanced by reducing the pressure level behind the membrane by adding a vacuum pump to create a limited under-pressure on the permeate side.

In this study we investigated methods to increase the concentration factors and/or the permeate flow rates in a straightforward manner. This paper provides experimental results for *vacuum-enhanced* dynamic cross-flow filtration in comparison with

the established *pulsation operation* mode. Additionally, for comparison reasons results for *open operation* mode as presented in [3] are highlighted.

4.3 Materials and Methods

4.3.1 Filtration Equipment

The Dynotest® by Bokela GmbH, Germany was used as filtration equipment. The unit has a 0.55 kW/ 400 V motor that drives a directly-coupled rotor in line with the axis of the filter disk. The cooled process chamber can be opened for cleaning and changing the membrane, as shown in Figure . The filtration area is 130 cm^2. The maximum filtration pressure is 7 bar (absolute).

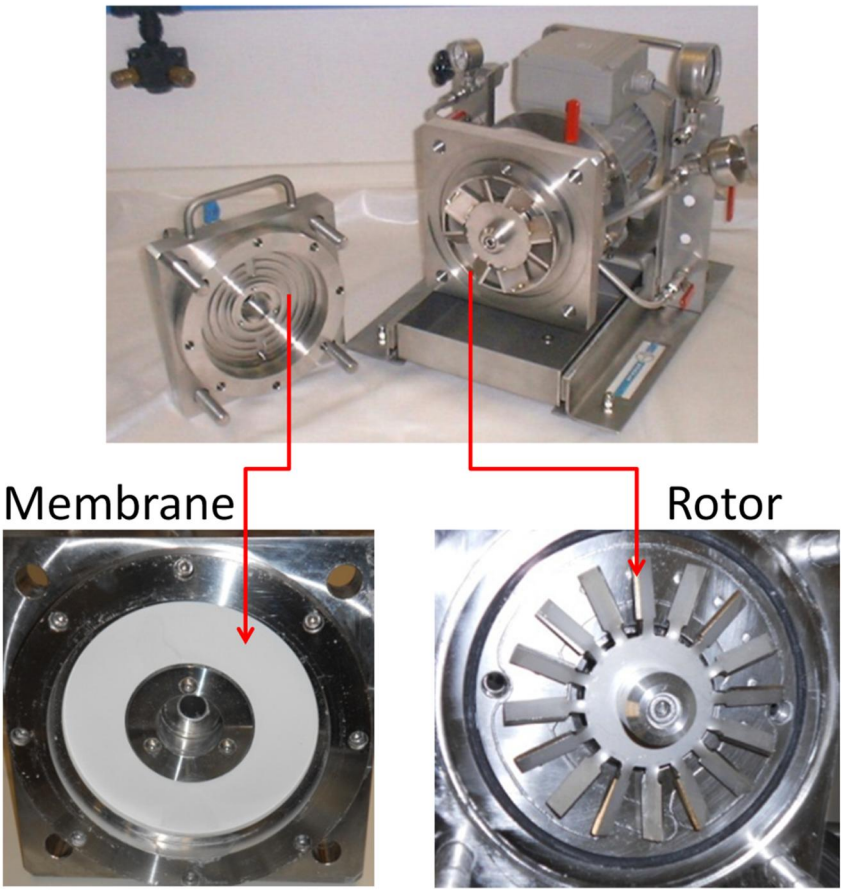

Figure 1 Pictures of the CFF (Dynotest® by Bokela GmbH) with rotor and ceramic membrane

A progressive cavity pump type MX10S-10/20® (Knoll Maschinenbau GmbH, Germany) was used to feed material into the process chamber. The feed throughput was

measured with smaller than 0.5% accuracy using an electromagnetic flow meter type FSM4000® by ABB GmbH. Permeate throughput was measured with 2.5% accuracy using an electromagnetic flow meter type 008AP001E® by Honsberg Instruments GmbH, Germany. To measure the filtration pressure, a pressure sensor type 261GS® by ABB GmbH with ±0.1% accuracy was installed. To enhance permeate flow rate, a peristaltic pump type ISM920® by Ismatec, Switzerland was added at the permeate outlet. A simplified P&I schema is provided in Figure 2.

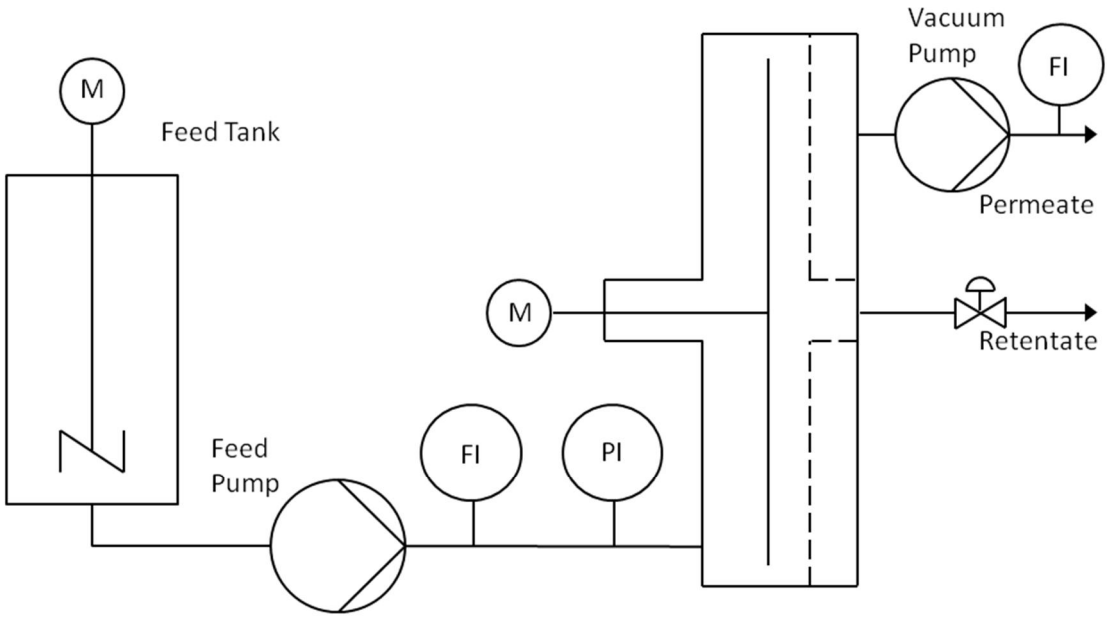

Figure 2 Schematic of the filtration setup

4.3.2 Materials

In our study, alpha-lactose monohydrate (Granulac_230® donated by Meggle AG, Austria) with a volume mean particle size of 19 µm was dispersed in water. To prevent particle size or shape changes due to dissolution, we used water saturated with pre-dissolved lactose (180 g/l). Ibuprofen with the volume mean particle size of 32 µm (BASF Switzerland) was also dispersed in water. In the case of Ibuprofen, 8 g sodium pyrophosphate tetrabasic (SPT) provided by Sigma-Aldrich were pre-dissolved per liter of water to ensure uniform dispersion. Solubility effects of Ibuprofen in water

are negligible. As membranes, aluminum oxide disks with mean pore size of 0.5 µm, inner diameter of 65 mm, outer diameter of 156 mm and thickness of 2 mm provided by Kerafol Keramische Folien GmbH, Germany were used.

4.3.3 Material Characterization

Raw materials and products were thoroughly characterized. Q3 particle size distribution (PSD), shown in Figure 3, was determined using laser diffraction with Helos® (Sympatec GmbH, Germany, dry dispersing unit Rhodos®) equipped with Sympatec Software, WINDOX 5.6.0.0®. The dispersion pressure was 1.5 bar.

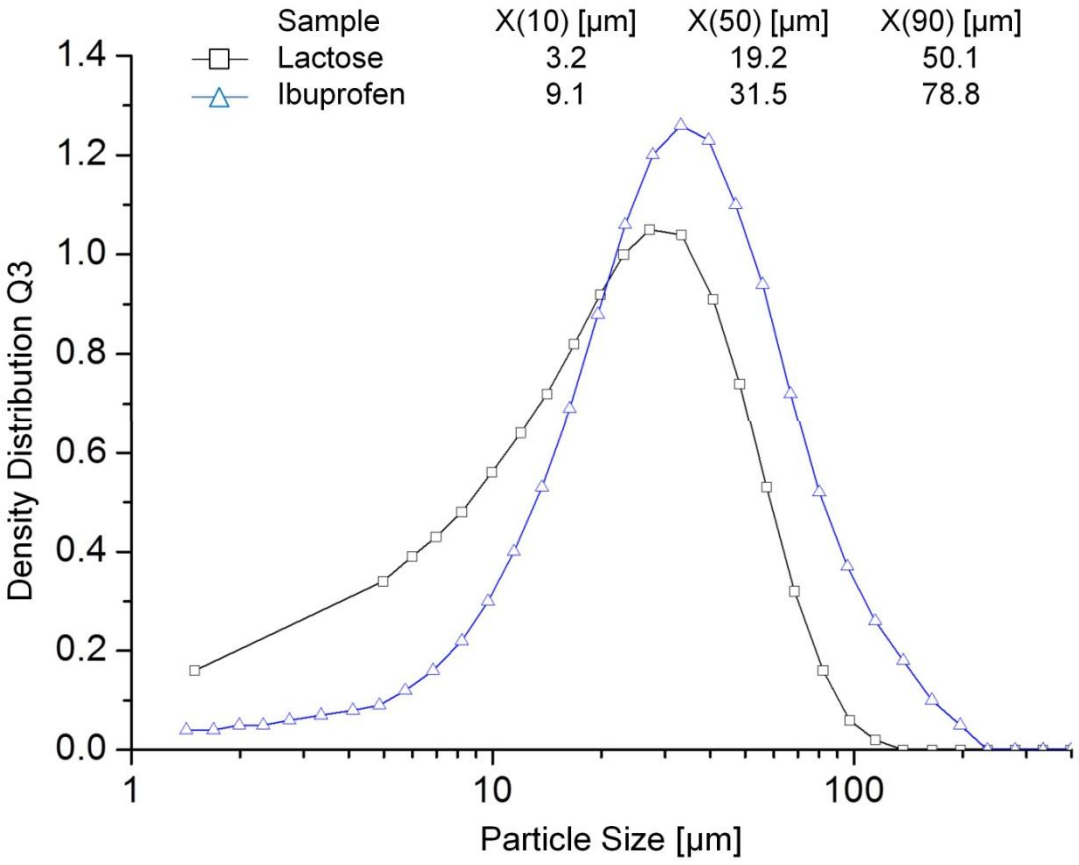

Figure 3 PSD of raw materials

Residual moisture was analyzed via a thermo-gravimetric method (MLS_N Version 2.0, Kern & Sohn GmbH, Germany). The drying temperatures for lactose and the Ibuprofen-SPT mixtures were kept constant at 105 °C and 65 °C, respectively. The final residual moisture content was determined once the weight did not change more than

1mg within 4 minutes, which corresponds to approximately 0.05 ‰ of relative weight change.

4.3.4 Methods

To avoid partial blockage of the membrane due to air enclosed in the internal membrane structure, prior to use all membranes were wetted in water for an hour. After assembly, the SFD was vented and rinsed with water for an hour to ensure evacuation of all air. During this time, the outlet valve was opened and a continuous operation mode was established in the *vacuum-enhanced operation* mode. In the *pulsation operation* mode, the outlet valve was kept closed during venting and rinsing. Subsequently, the feed was switched from water to suspension. Suspension was prepared in a continuously stirred tank and fed to the SFD via a progressive cavity pump.

In the *vacuum-enhanced operation* mode, the rotation speed of the peristaltic pump (permeate side) was increased stepwise to prevent transgression of maximal solid concentration levels as defined by a ramp-up test, which would lead to blockage of the rotor. At maximum rotation speed (130 rpm) an additional pressure difference of approximately 0.54 bar could be achieved. The additional pressure difference was calculated using Equation 6, and the permeate flow and the membrane resistance were measured with water only. The measured chamber pressure of 1.41 bar was typical for the open operation mode.[3] Thus, a total pressure difference of 0.95 bar were achieved by the vacuum pump speed of 130 rpm and the SFD rotor speed of 1400 rpm.

In the *pulsation* mode, the retentate valve was designed to open once a material-specific rotor load set point was reached. For lactose and ibuprofen, the opening set points were 71.5 W and 60.5 W, respectively, with open valve intervals of 0.7 s in both cases. These set points were determined by ramp-up tests, during which the retentate valve was kept closed and the suspension was continuously fed to the chamber. As the permeate continuously exited the process chamber, both the suspension's solid concentration in the chamber and the rotor load (measured via frequency converter) increased. As shown in Figure 4, in the beginning of the ramp-up test, the ro-

tor load increased slowly. Once a certain solid concentration in the process chamber was reached, a rapid rise in the rotor load occurred. The rotor load set point was chosen in the beginning of the rapid load increase. After this point, a slight increase in the solid concentration led to a fast increase in the rotor load. To minimize the risk of rotor blockage, the rotor load set point should not be exceeded.

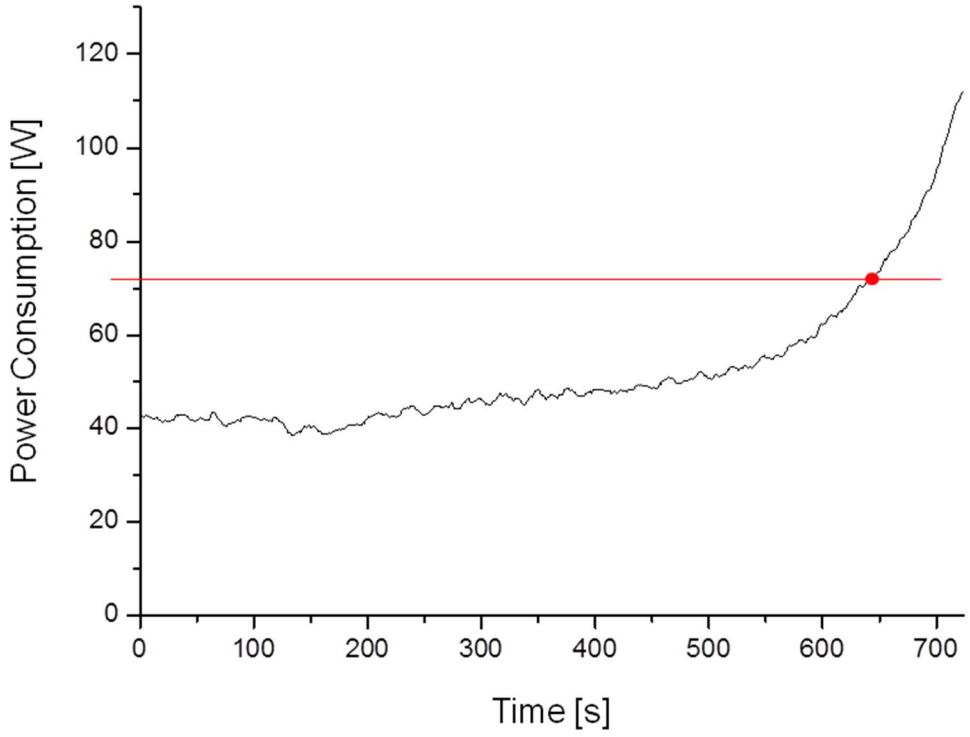

Figure 4 Ramp-up test for lactose to determine rotor load setpoint

Tests were performed for all three operation modes, as shown in Table . Since rotor blockage occurs once a certain solid concentration in the filtration chamber is exceeded (50wt % for Ibuprofen and 76 wt% for lactose), a low level of feed solid concentration was chosen to demonstrate the possibility of achieving high CFs. Therefore, suspension concentrations range from 10-20 wt%. The feed flow rate was set to 4 kg/h, which is a typical small-scale throughput, while at the same time preventing sedimentation in the feed pipes in our lab setup. The rotor speed was set to 1400 rpm (the maximal rotation speed) to ensure the most efficient CPL removal and the highest permeate rates and retentate solid concentrations.

The residual moisture of the steady-state product was calculated based on the feed and permeate flow measurements. Additionally, product samples were dried in a

thermo-gravimetric balance. The concentration factor (CF) was calculated according to Equation 5 [15] as the ratio between product and feed concentration.

4.4 Results

A summary of the results as well as the tested parameter range is shown in Table 1.

Table 1 Tested parameter range with resulting retentate solid concentration and concentration factor (CF)

Substance	Operation mode	Feed flow [l/h]	Feed solid concentration [wt%]	Retentate solid concentration [wt%]	CF
Lactose	Open mode	4	10	17	1.7
	Vacuum-enhanced open mode	4	20	70	3.5*
	Pulsation mode	4	10	76	7.6*
Ibuprofen	Open mode	4	10	20	2.0
	Vacuum-enhanced open mode	4	20	52	2.6*
	Pulsation mode	4	10	50	5.0*

* Concentration factors for the *pulsation* and *vacuum-enhanced operation* modes strongly depend on the feed concentration. In order to reach a specific maximal concentration defined by the rotor load set point, in the *pulsation* mode retentate valve opening is controlled and in the *vacuum-enhanced operation* mode vacuum pump speed is adapted.

4.4.1 Open Operation Mode

In the open operation mode, a material-dependent, yet otherwise constant CF (1.7 for lactose; 2 for Ibuprofen) is obtained. As reported in [3], typical startup times to reach steady-state are from 45 minutes to an hour. In all *open* mode runs, the transmembrane pressure reached a constant level of 1.41 bar after the startup phase, with centrifugal forces of the rotor causing the largest fraction of the measured pressure level.

4.4.2 Vacuum-Enhanced Operation Mode

In the *vacuum-enhanced open* mode, maximal pressure difference was 0.95 bar (1.41 bar measured chamber pressure plus vacuum). Fluctuations in the permeate flow (Figure 5 and Figure 6) result from variations in the vacuum pump rotation speed that were introduced in order to keep CF high but to avoid transcending maxi-

mal solid concentration levels as defined by a ramp-up test. Additional adaptations of vacuum pump rotation speed were necessary to compensate for false air aspiration into the vacuum system. The aspiration of false air caused declines of vacuum conditions as well as deviations in the permeate flow measurement. Achievable CFs in the *vacuum-enhanced* open mode were approximately 3.5 for lactose and 2.6 for Ibuprofen, and thus approximately 2.1 and 1.3 higher than in the open mode. CF values are calculated using initial feed solid concentrations. As the vacuum level was adapted to achieve maximal retentate solid concentrations (as determined by a ramp-up test) calculated CF values would be higher for lower feed solid concentrations.

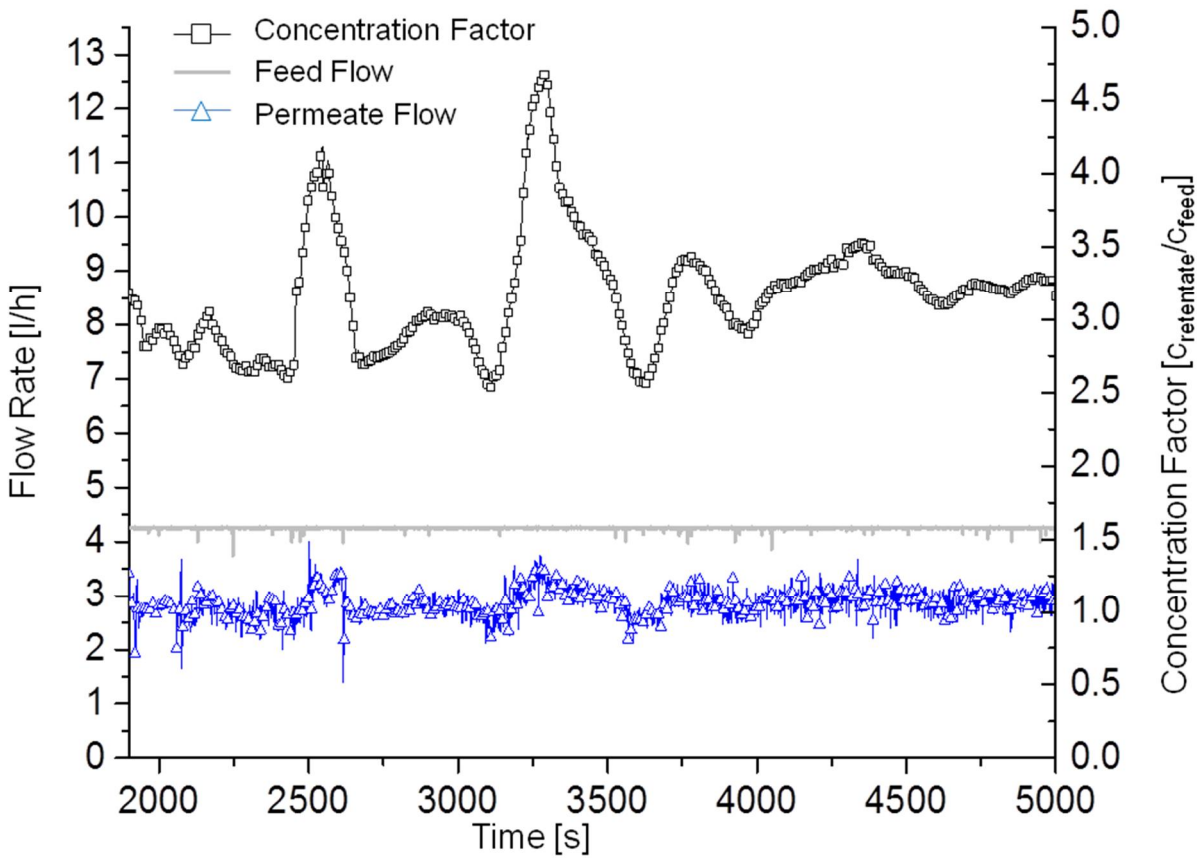

Figure 5 Experimental results for the vacuum-enhanced open operation mode with lactose (only every 10th data point plotted). The large fluctuations in the permeate flow and in CF from 2000 to 4000 s result from variations in the vacuum pump speed. During this time span, the vacuum pump speed was manually manipulated to maximize CF while avoiding transgression of maximal solid concentration levels as defined by a ramp-up test

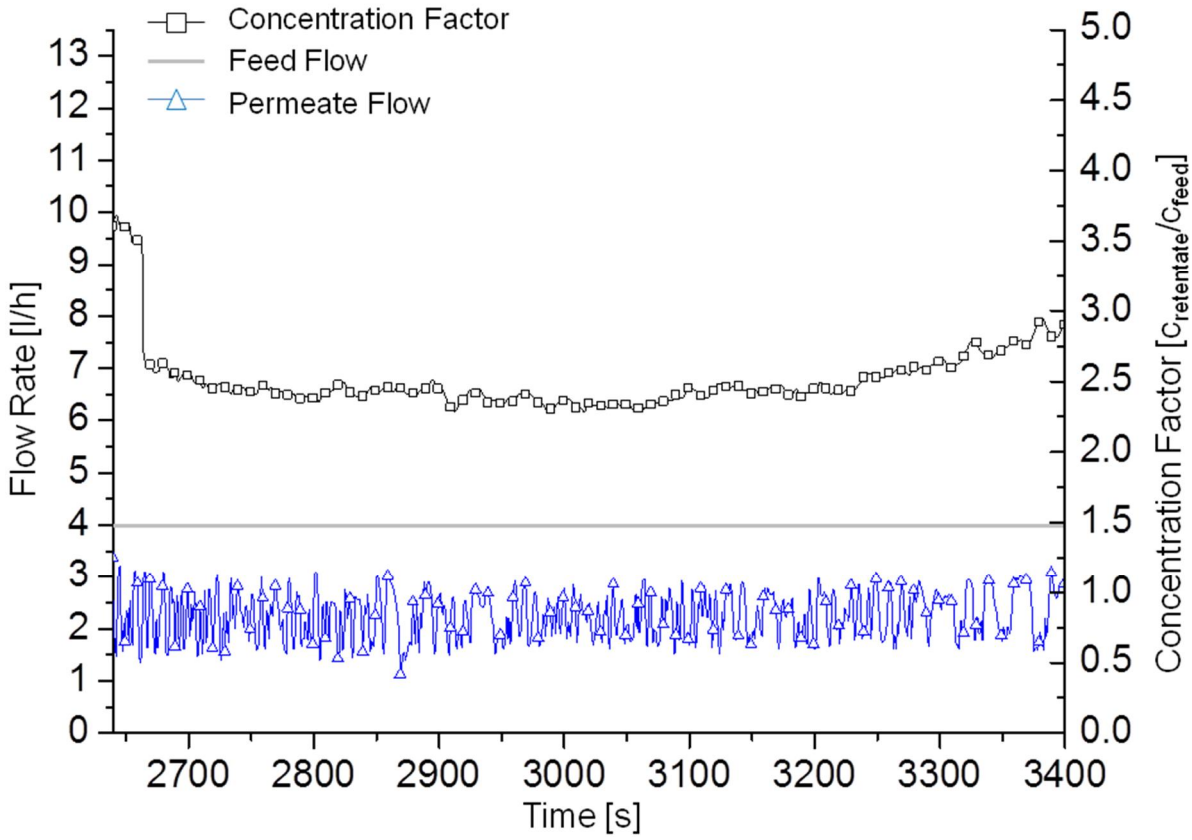

Figure 6 Experimental results for vacuum-enhanced open operation mode with Ibuprofen (only every 10th data point plotted)

4.4.3 Pulsation Operation Mode

In the *pulsation* mode, the pressure remained at 1.4 bar for lactose, as shown in Figure 7. However, an additional test run performed at an elevated feed rate of 8 kg/h resulted in a pressure increase of 1.8 bar. For Ibuprofen, even at a feed rate of 4 kg/h, a rise in the pressure to approximately 2 bar was observed (Figure 8). Achievable CFs in the *pulsation* mode were 7.6 for lactose and 5 for Ibuprofen. As retentate solid concentration solely depends on a material depended rotor load set point determined in a ramp-up test, calculated CF values only depend on feed solid concentrations. As for the vacuum enhanced operation mode, achievable CF values would be higher for lower feed solid concentrations.

In Figure 7 and Figure 8 measured chamber pressure difference is shown instead of CF. As retentate solid concentrations reached a constant value right from the start

(76 wt% for Lactose and 50 wt% for Ibuprofen), CF values were also constant. In contrast, chamber pressure was subjected to constant pressure rises and decreases due to repeated opening and closing of the retentate valve.

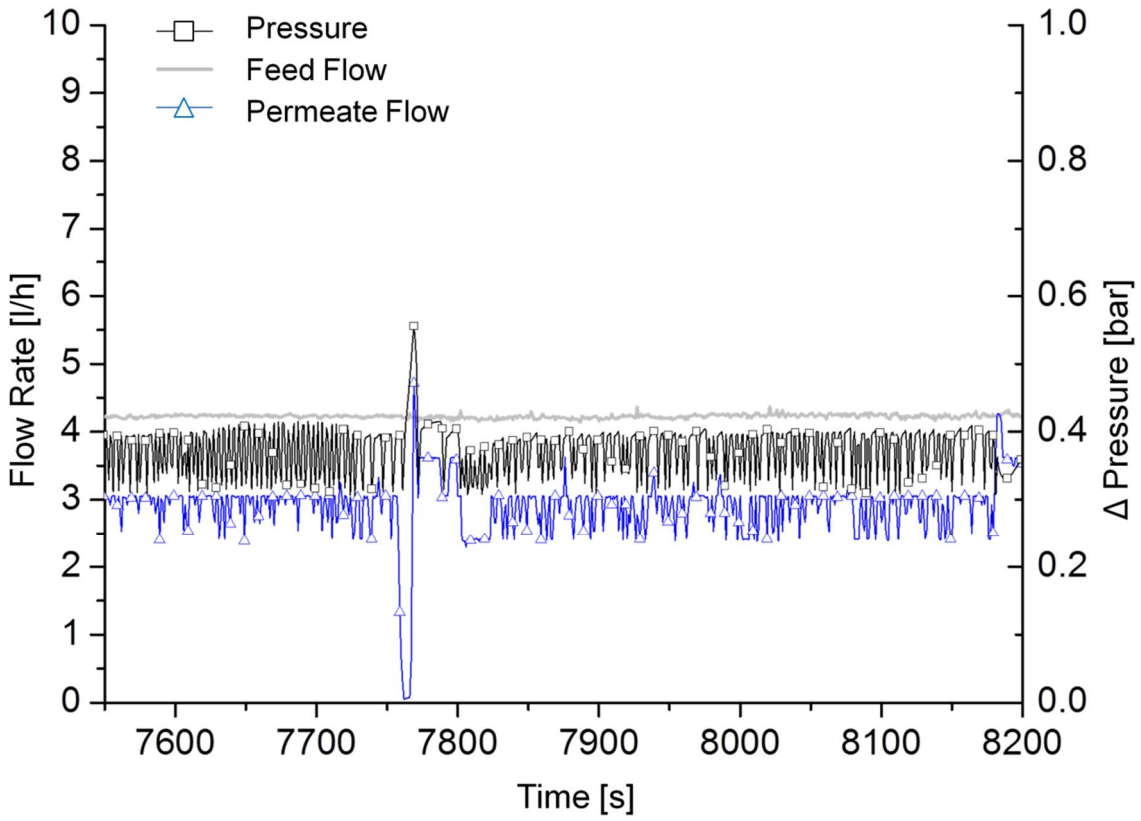

Figure 7 Experimental results for pulsation operation mode with lactose (only every 10th data point plotted) The peak measured at 7760 seconds results from a short term material congestion at the retentate valve. However, the subsequent pressure rise sufficiently removed the congestion

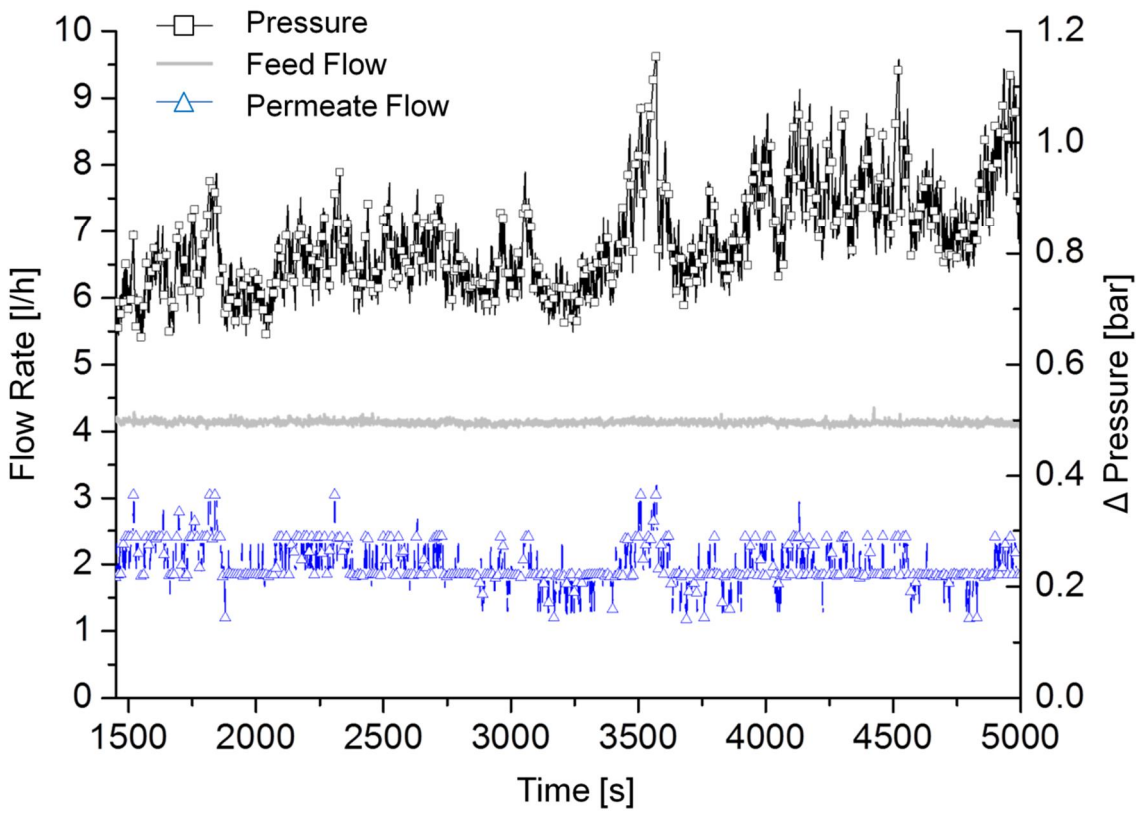

Figure 8 Experimental results for pulsation operation mode with Ibuprofen (only every 10th data point plotted)

4.5 Discussion

As reported in,[3] the open operation mode requires long start-up times for obtaining a constant concentration polarization layer (CPL). During the start-up phase, variations in the concentration factor, i.e., variations in the retentate moisture level, can be expected. Depending on the feed rate, this can lead to a large amount of reject material or material that needs to be re-treated. However, once the steady state is reached, highly stable flow rates and CFs are obtained. Since the CFs depend exclusively on the material, they are constant over a wide range of flow rates and feed concentrations, as described in.[3] This means that filtration, which involves achieving a significant concentration increase, may require a high number of subsequent filtration steps. This requires additional production equipment or time-consuming recycling steps and results in a large amount of reject material during each start-up phase.

Time to steady state can be significantly reduced in the *vacuum-enhanced* open mode. For the manually operated vacuum system, a slow stepwise increase in the vacuum level was required to avoid transcending maximal solid concentration levels as defined by a ramp-up test and subsequent blockage of the filter rotor (Figure 5 from 2000 to 4000 seconds). Shorter times to steady state can be expected when setting up an automated control of the vacuum system. In addition, by ensuring a constant vacuum level, fluctuations in the permeate flow can be reduced. In our experiments, air slip into the vacuum system caused a decline in the vacuum conditions and deviations in the permeate flow measurement. Less permeate flow fluctuations can be expected when using a vacuum pump type other than the implemented peristaltic pump. Since the vacuum system can be used to control the permeate flow, in a fully automated system a constant CF can be achieved from the start of operation, i.e., only a small amount of initial retentate will have to be discarded (or re-treated). This small amount results from the fact that the implemented system has to be prefilled for degassing purposes; therefore initial retentate consists of a mix of prefilled liquid and feed material. As shown in Table , the achievable concentration factors were quite high, and the final solid concentration matched the maximum final solid concentration determined during the ramp-up tests.

In the *vacuum-enhanced operation* mode, one filtration step was enough to reach the maximum final concentration levels. This may not be the case for substances that are prone to a reduction in the permeate flux at elevated vacuum levels, e.g., due to compaction of the CPL layer. However, compared to the open mode operation, an increase in the CF for most materials (as was the case for all tested substances) and less filtration equipment or recycle circles can be expected.

Start-up time in the *pulsation* mode depends solely on the feed rate: the faster the filtration chamber is filled, the sooner the predetermined rotor load set point is reached and the retentate valve opens. Due to the regulated product discharge, the maximal final solid concentration is reached in one step and the retentate has a constant solid concentration right from the beginning. Due to the intermittent closure of

the retentate valve and the retention of the concentrated product, the system pressure rises. According to Equation 6, a rise in the pressure results in an increased permeate flow rates, as long as there are no additional effects, such as the compaction of the CPL layer. During our experiments, a pressure rise to approximately 2 bar was observed before the system stabilized. Although the pulsing nature of the retentate flow may cause variations in subsequent manufacturing steps, e.g., drying and mixing, its direct integration into downstream steps without buffers may be feasible. For this purpose, the retentate stream has to be well characterized, i.e., the retentate flow rate has to be precisely determined. Calculation of retentate flow rate from permeate measurement is inaccurate (calculation with mean values), therefore retentate flow rate has to be measured directly. For most flow measurement devices this is difficult to achieve at low flow rates, especially if the monitored fluid is a highly concentrated slurry.

4.6 Conclusion

Three operation modes were tested using the same continuously or semi-continuously operating cross-flow filtration device and two model substances. Process stability, the ability to integrate with downstream steps and the filtration efficiency (high achievable suspension concentration) are key factors in choosing an operation mode.

Fluctuating feed rates and concentrations cannot be compensated in the *open operation* mode since the only controlling parameter is the CPL layer or rather the CPL layer buildup.[3] Fast fluctuations cannot be compensated quickly by variations in the CPL layer. As such, variations in the feed flow will result in variations in the retentate composition. In the *vacuum-enhanced operation* mode, the vacuum level can be adapted by a control system, reacting to the changing feed conditions. Thus, changes in the feed concentration and feed flow rate can be accounted for and variations in the retentate composition can be avoided. Since in the *pulsing* mode the retentate valve only opens once a given rotor load/chamber solid concentration is reached,

retentate composition does not depend on the feed conditions and the only variation in the retentate is the resulting flow rate over time.

The pulsating output flows (flow rate and pressure) of this operation mode pose challenges for integration in subsequent manufacturing steps. Buffering might be needed, or retentate flow rates have to be measured directly. However, measurement of fast changing high viscosity suspensions at low throughput volumes is challenging. In contrast, retentate flow rates in the *open* and *vacuum-enhanced operation* modes can be characterized using the permeate flow rates. Even direct measurement of the retentate stream is possible due to the constant flow through cross-flow filtration equipment.

In terms of achievable CFs, the *pulsation* and *vacuum-enhanced operation* modes are superior to the open operation mode. Minimizing the number of required filters decreases not only the investment costs, but also possible sources of error. In this context, the open operation mode seems to be the least beneficial: for example, low feed concentrations would necessitate a large number of filtration steps or filtration cycles. Depending on the filtered substance, the *vacuum-enhanced operation* or *pulsation operation* modes with the increasing filtration pressure may result in higher CFs. For several substances permeability of the concentration polarization layer is known to decrease once a certain vacuum or pressure level is reached. For the tested lactose and Ibuprofen-water mixtures no significant differences could be observed with driving pressure forces reaching approximately the same values (vacuum enhanced mode: 1.95 bar; *pulsation* mode: 1.8 bar for lactose and 2 bar for Ibuprofen). Therefore, both operation modes seem feasible, according to the specific filtration characteristic of the treated substance.

Overall, the *vacuum-enhanced operation* mode appears to be the most promising one in terms of achievable CFs for a large number of substances. Easy integration into subsequent manufacturing steps, straightforward flow monitoring and fast reaction to changes in the feed conditions make this operation mode promising for enhanced continuous small-scale filtration.

4.7 Acknowledgements

We would like to acknowledge the support of Manuel Zettl, Daniel Wiegele, Arlin Gruber and Daniel Kaiser and thank Bokela GmbH for their assistance, Meggle AG for donating lactose and Novartis Pharma AG Basel for financial contribution.

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5. Continuous Drying of Small Particles for Pharmaceutical Applications: An Evaluation of Selected Labscale Systems[6]

5.1 Abstract

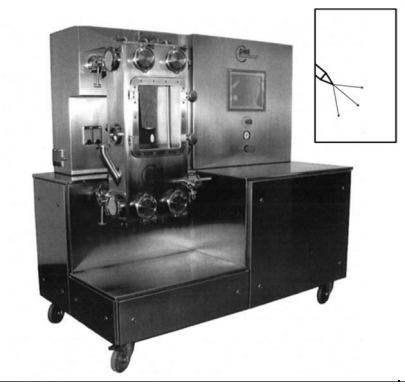
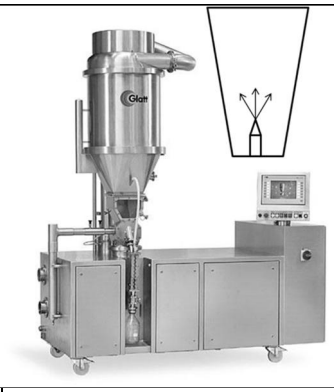
Moving towards continuous manufacturing in the pharmaceutical industry offers new possibilities, such as reducing costs and improving product quality. However, this paradigm change requires new small-scale continuous manufacturing technologies. Since drying is one of the crucial elements of pharmaceutical production, we performed an evaluation of existing drying technologies suitable for continuous production. We focused on small-scale equipment for handling pre-concentrated slurries at the kg/h scale. Lactose (soluble) and Ibuprofen (poorly soluble) suspensions were dried, first, in two fluidized bed spray dryers, second, in a small-scale spray dryer, third, in a spin flash dryer, fourth, in a paddle dryer and, finally, in an co-rotating twin-screw extruder. During these trials we evaluated the performance of the equipment and its advantages and disadvantages with regard to pharmaceutical production. A utility analysis was performed to compare the different technologies. The results confirm that there is a lack of continuous small-scale equipment for drying crystalline products without causing agglomeration and/or attrition in order to preserve crystal properties originating from careful en-

[6] This chapter is based on: J.S. Gursch, R. Hohl, M. E. Armenante, D. Dujmovic, S. Sacher, P. van der Wel, J. Brozio, M. Krumme, N. Rasenack, J.G. Khinast "Continuous Drying of Small Particles for Pharmaceutical Applications – An Evaluation of Selected Labscale Systems", Drug Development and Industrial Pharmacy, submitted

gineering during the crystallization phase. The aim of this study was to provide information regarding operational capabilities of continuous small-scale drying equipment.

5.2 Graphical abstract

Evaluation of 5 continuous lab scale drying technologies

1 Fluidized bed spray dryer		2 Spin flash dryer
		
3 Spray dryer	4 paddle dryer	5 Extruder
		

5.3 Introduction

Continuous manufacturing in the pharmaceutical industry promises not only reduced manufacturing costs but also increased product quality, flexibility and agility [1] and is an important step towards 24 h automated production.[2] However, since continuous manufacturing is a relatively new approach to pharmaceutical production, process development costs remain high. In particular, the absence of classical batches, which can easily be accepted or rejected, requires a high level of process control and a new regulatory approach.[2] Process analytical tools must thus be used extensively to guarantee continuous process analysis and control.[3]

Nevertheless, development time for continuous processes can often be shortened as they make scale-up predictable, thus reducing time to market and speeding up the supply chain.[4] In a continuous environment, scale-up can be done by simply extending the process into the fourth dimension, i.e., the process time.[2] This allows use of the same equipment for small-scale clinical trials, for formulation research and for the development of the final production process. Furthermore, continuous processing equipment has a smaller footprint and smaller operating costs [5] and can simplify manufacturing procedures.[2] Continuous flow chemistry makes rapid quenching of highly exothermic and/or hazardous reactions possible,[6] creating reaction pathways that are impossible in the batch mode or helping to eliminate unwanted side reactions.[3] This is because higher surface-area-to-volume ratios facilitate better heat transfer and faster mixing. Moreover, as reactor size is usually smaller in continuous production plants, smaller amounts of material are active e.g., in chemical reactions, which makes processes safer and expedites the changes for multipurpose plants.[7],[4]

The existing continuous manufacturing equipment in the chemical or food industry, however, is designed mostly for large-scale production.[2] For example, powder feeders have been designed for a kilogram-per-hour rate (at the very minimum) and above. Reliable feeders that continuously and accurately dose grams per hour have yet to be developed. This is also true for drying, where current technology lacks equipment for handling small process streams. Yet drying and solvent removal are crucial steps in pharmaceutical manufacturing.[8] Crystalline active pharmaceutical ingredient (API) production must guarantee that the crystals are not damaged or modified during drying. Thus, for many applications, the drying step is critical.[9]

In this study, we focus on continuous drying of pharmaceutical compounds. To keep energy consumption low it is generally advisable to mechanically remove as much of the solvent as possible before thermal drying [10], [11], i.e., by filtration. This observation creates a demand for continuous drying equipment that can handle highly viscous preconcentrated slurry. The purpose of this review is to identify and evaluate the available continuous small-scale drying equipment that can meet the pharmaceutical industry's new demands. We concentrate on multi-purpose equipment for handling lab-scale process streams and evaluate the equipment using two organic substances that are typical

for the pharmaceutical industry: lactose (two grades) and Ibuprofen. Even though there is a large variety of drying technologies available on the market e.g., belt dryers, infrared dryers, thin film dryers etc., only few are apt to continuously dry lab scale volumes of multiple viscous pre-concentrated products. In this review, we present five drying technologies that were studied. Each technologies performance during our test is analyzed individually. In the last section of this paper a comparative evaluation is made based on the results of our experiments.

5.3.1 Fluidized bed spray dryers

Fluid-bed drying is a common application of fluidized bed systems in large-scale production lines for raw materials and foods (e.g., Glatt GF/ AGT series, GEA Niro contact-/ vibro-/ spray fluidizer, DMR WFO 15-2, etc.). Fluidized bed systems operate by uniformly distributing a gas throughout a particle bed to give it liquid-like properties.[12] In this study a special type of fluidized bed dryer was investigated, namely a fluidized bed spray dryer. As suggested by its name the analyzed setup exhibits large similitude to spray drying. During fluidized-bed spray drying, a continuous feed spray is introduced into a chamber, also allowing liquid suspensions to be dried in a fluidized bed. In this process droplets are created via spray drying. The droplets are suspended in the fluidized bed where they dry until required residual moisture levels are reached. If direct fluidization of the spray dried material is not possible, fluidized bed agglomeration/ coating represent an alternative route. In this case seed particles are used on which the liquid can be sprayed.[13] Tiny droplets are applied to the suspended fluidized bed particles as they pass by the nozzle atomizer. The droplets then dry and can form two distinct particle structures, either agglomerates or onion-like granules, depending on the liquid properties (e.g., viscosity), the presence of a binding agent and the size of the particles present in the fluidized bed. Dried product is discharged continuously at the end of the process chamber using e.g., rotary or oscillating valves or zigzag sifters.

The range of products that can be produced makes fluidized-bed spray drying systems a practical tool for the pharmaceutical industry, since it can be adapted to meet various product requirements.[14],[15] Moreover, the systems have few or no moving parts,

requiring little maintenance. [16] However, it is difficult to dry very fine powders. Pharmaceutical granular materials typically have sizes ranging from 1 micron to 1 cm.[12] Best particle size for smooth fluidization ranges from 40 to 1000 µm [12] based on Geldart's classification.[17],[18] Larger particles require spouted bed fluidization . Smaller particle may not fluidize at all and form channels for air flow. One disadvantage of fluid-bed systems is that they require a significant amount of pre-treated process air.
In our work, two fluidized bed spray drying devices were tested with regard to fine powder manufacturing for the pharmaceutical industry.

5.3.2 Spray dryers

Spray drying is widely used in the industry due to its wide range of applications and suitability for continuous production. In contrast to the systems described in 1.1, no fluidized bed is created and maintained. Various processing alternatives exist, from simple drying of a suspension to microencapsulation of particles for obtaining special properties that may increase solubility, mask tastes and smell or can optimize handling.[19],[20]

In the process a spray of the liquid solution or a suspension is created and the droplets fall through the process chamber and dry in hot air (or an inert atmosphere).[21] The powder is eventually separated from the air using a cyclone. Unique for spray drying is the fact that the end product can be an amorphous or a crystalline structure [22] as during the fast drying of a solution precipitation and/or crystallization occur. Particle shape and structure can be controlled by changing the prevalent drying kinetics and droplet size.[21] Adaptations can range from changes of the feed liquid composition to implementation of different nozzle or rotary atomizers types, or simply changes in spray pressure, temperature and air flow.[23] The obtainable final particle size ranges from a few to 250 µm.[24],[25] Even nano-particles may be obtained (e.g., Büchi nano spray dryer B-90). Spray drying is suitable for drying thermally sensitive materials and maintaining good product quality as the drying time is relatively short and the product experiences lower temperatures than the drying gas temperature. This applies especially to co-current spray drying as only fresh material with high residual moisture is exposed to

the drying air inlet temperature. While particles are moving through the spray chamber, the surrounding drying air temperature is constantly reduced according to the amount of liquid evaporated. Very thermo-sensitive or sticky products can be processed in freeze spray dryers.[26]

To establish a general understanding of the possibilities and limitations of spray drying equipment, tests were performed using a standard lab scale spray dryer as described in the following section.

5.3.3 Spin flash dryers

Flash dryers are designed for the fast drying of wet particles with surface water. It is a drying method where hot air and a high relative velocity between particles and air increase the drying rate. During this process fast drying is achieved by dispersing the wet material in a high velocity air stream. Whereas typical flash drying systems are often restricted to drying moist granular materials or particles, the spin flash dryer, featuring an extra chamber with spinning blades, can also process heavier pastes and slurries.[27] Due to the spinning blades, agglomerates are destroyed and the surface area of every particle is exposed, resulting in high levels of heat and mass transfer and drying rates.[28] In this system, wet particulate material, delivered by a screw or another device, is fed into a vertical drying duct with hot air flow and rotating blades at the lower part of the drying chamber. As the paste enters the chamber, the impact energy of the blades breaks agglomerates into smaller primary particles, which are further reduced in size through numerous collisions and dried as they move around the bottom of the chamber, thereby creating a mechanically agitated fluidized bed with a short residence time.[28] Once a low enough mass is attained, particles flow upwards through the drying chamber. A cyclone is used to separate the dried particles from the air. In our study a small-scale spin flash dryer was used to investigate the effects that the blade speed, airflow, flange size and temperature had on the product's particle size and quality.

5.3.4 Paddle dryers

Paddle dryers are typical contact dryers commonly used for drying sludge in many industries.[29] They consist of a heated cylindrical housing with a rotating horizontal agitator, whose paddles constantly stir the drying material and move it through the dryer. That is, movement through the dryer is achieved through mechanical agitation by the dryer paddles in contrast to 5.3.3 spin flash dryers where transport is achieved by the drying air flow. The robust equipment design and the high shear allow sticky and lumpy solids to be processed.[9] In most drying systems material crust buildups in the housing are generally undesirable as they decrease drying rates.[30] In the paddle dryer tested in this evaluation the feed is in constant contact with a heated wall to form such a crust. During drying, the crust disintegrates and falls into the process chamber. The rotating paddles grind the crust into smaller pieces and contact with the wall is established again where drying continues. The final dryness of the product depends on the temperature and length of the tube and on the paddle inclination. Due to a high rotation rate of the paddles (600 to 1000 rpm), the investigated paddle dryer could only handle highly viscous products, since low-viscosity products would be transported to the outlet too quickly.

5.3.5 Extruders

Especially in the food and plastic industry, extrusion has been long established as an inherently continuous process.[31],[32] Extruders blend, compound, granulate or melt materials which are extruded through a die plate to form a strand of material that can be spheronized or cut with the corresponding equipment.[33],[34] In some cases (wet granulation) the die plate is omitted. Drying in an extruder has been performed as well, for example in polymer treatment.[35],[36] Nowadays extruders are also increasingly used for drug production.[37],[38],[39] In drug manufacturing, a narrow residence time distribution is important to allow a precise definition of a batch.[2] Moreover, the overall residence time in hot-melt extrusion should be short to avoid product degradation. This problem can easily be solved by using twin screw extruders whose intertwining screws are self-cleaning.[40] A residence time in the order of one to a few minutes can

be achieved. In addition, material transport through extruders can be controlled well. Furthermore, an extruder can process various feeds ranging from solids to pastes.[41] Therefore extruders can also be used as driers for many applications. This principle has been used by us for the drying of pasty materials.

5.4 Materials and Methods

5.4.1 Materials

In our work two different model compounds, i.e., lactose and Ibuprofen, were used. Thus, one compound is very soluble (lactose) the other one not (Ibuprofen). For lactose qualities (both alpha-lactose monohydrates), i.e., Sorbolac_400 with the volume mean particle size of 8 µm and Granulac_200 with the volume mean particle size of 34 µm provided by Meggle AG, Austria were considered. These materials were dispersed in water. To prevent changes of particle size or shape due to partial dissolution, water saturated with pre-dissolved lactose (180 g/l) was used.

Ibuprofen_25 with the volume mean particle size of 34 µm, from BASF Germany, was also dispersed in water. In the case of Ibuprofen, 8 g sodium pyrophosphate tetrabasic (SPT) per liter provided by Sigma-Aldrich were pre-dissolved to ensure uniform dispersion. Solubility of Ibuprofen in water is low and was thus neglected. For the fluidized bed spray drying runs, 4 wt% Mowiol© 40-88 from Sigma-Aldrich were added to the suspensions as a binder to facilitate granule formation. Concentrations are given in wt% solid, based on total mass.

Thus, in summary three materials were used for the tests.

5.4.2 Material characterization

Raw materials and products were thoroughly characterized. The Q3 particle size distribution (PSD) was determined using laser diffraction via Helos (Sympatec GmbH, Clausthal-Zellerfeld/Germany, dry dispersing unit Rhodos) equipped with Sympatec Software, WINDOX 5.6.0.0. The dispersion pressure was 1.5 bar. The Frauenhofer ap-

proximation method and the MIEE equation algorithm were used for Ibuprofen and lactose, respectively. The particle surfaces and shapes were examined with a scanning electron microscope (SEM) (VEGA 3 SEM, TESCAN, Brno, Czech Republic) operating at 10-20 kV. All samples were gold-sputtered (Sputter Coater 108auto, Cressington, Watford, England).

To determine the effect of SPT on the melting point of Ibuprofen, differential scanning calorimetry (DSC) (204F1 Phoenix, Netzsch GmbH, Selb, Germany) was performed. Powder samples were placed into pierced aluminum cubicles purged with pure nitrogen. The scanning rate for all samples was 5 K/min at 25-120 °C.

Residual moisture was analyzed using a thermogravimetric method (MLS_N Version 2.0, Kern & Sohn GmbH, Balingen, Germany). The drying temperatures for lactose and for the Ibuprofen-SPT mixtures were kept constant at 105 °C and 65 °C, respectively. The final residual moisture content was determined after 240 s of weight consistency smaller than 1 mg. Concentrations are given in wt% solid, based on total mass.

5.4.3 Drying Methods

Drying tests were performed in (1) two different fluidized-bed spray dryers, (2) a small-scale spray dryer, (3) a spin flash dryer, (4) a paddle dryer and (5) a twin-screw extruder. The equipment and the process-specific test setups are described in the following subsections. The maximum material temperatures during all tests were 80 °C for lactose and 65 °C for the Ibuprofen-SPT mixtures.

5.4.3.1 Fluidized bed spray dryers

Two fluidized bed spray dryer systems were investigated. The first one was a WFP-Koni (DMR Prozesstechnologie GmbH, Kaiseraugst, Schwizerland) with a rectangular process chamber and throughput of 1-15 kg dry product/h. The DMR equipment was used in a top-spray configuration (Figure 1) with the feed nozzle atomizer spraying from the upper corner of the process chamber, towards the lower corner of the other side and down

onto the fluidized particle bed. Dry granules were ejected by periodically opening the bottom-end hatch.

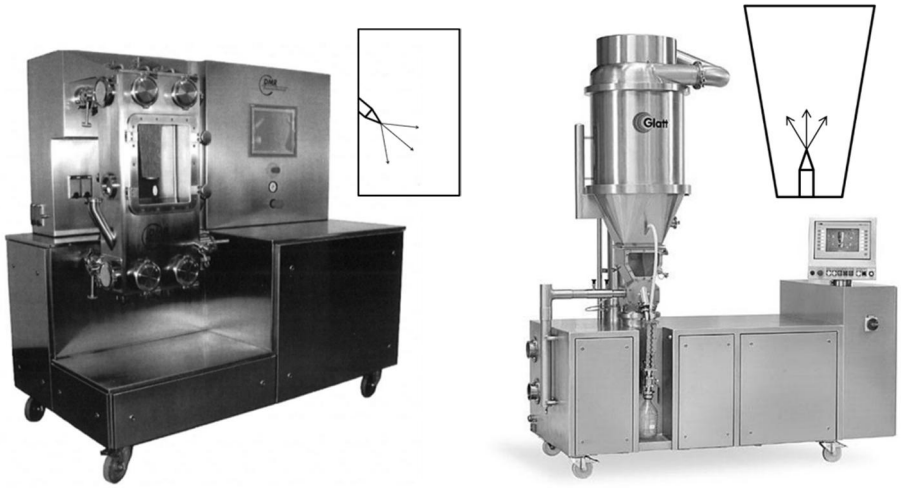


Figure 1 From left to right: WFP-Koni from DMR with a schematic drawing of the top-spray configuration, GF 5 ProCell lab System from Glatt with a schematic drawing of the bottom-spray configuration. Spray configurations are adaptable on both systems

The second setup was a GF 5 ProCell Lab System (Glatt Ingenieurtechnik GmbH, Weimar, Germany) with a cylindrical process chamber and throughput from 0.2-15 kg dry product/h. The Glatt system operated in a bottom-spray configuration (Figure 1) with the feed nozzle atomizer spraying from below the fluidized bed into the fluidized particles. According to literature, the bottom-spray configurations produce more regular granules in comparison to a top-sprayed product.[42] The product was discharged via a zigzag sifter at the bottom of the process chamber, with fines returned into the process chamber.

The first experiments performed on both systems determined the maximum sprayable concentration levels of the tested suspensions. For this purpose, the lactose and Ibuprofen suspensions were prepared at varying concentration levels. The maximum sprayable concentration levels were determined according to DMR's and Glatt's system guidelines. All of the following tests were performed at the maximum concentration level, as indicated in Table 1.

Table 1 Tested parameter range during fluidized bed drying

		Lactose (quality Sorbolac)		Ibuprofen	
		DMR	Glatt	DMR	Glatt
Maximum sprayable concentration [wt%]		47	50	18	26
Spray rate [g/min]		10 - 32	12 - 45	3 – 11	10 – 23
Drying air throughput [m^3N/h]		110 – 150	40 - 80	80 – 140	50 - 80
Drying air pressure difference [mbar]		4 – 12	5 – 20	3 – 6	Na*
Drying air inlet temperature [°C]		80	35 - 80	45 – 80	50 -70
Exhaust air temperature [°C]		42 – 55	25 - 38	37 – 40	23 – 30
Product temperature [°C]		48 - 57	25 - 43	38 – 44	25 - 35
Test run #1	Amount of receiver [g] Amount of binder [wt%]	0 0	0 0	0 0	0 0
Test run #2	Amount of receiver [g] Amount of binder [wt%]	500 0	300 0	500 0	430 0
Test run #3	Amount of receiver [g] Amount of binder [wt%]	not tested	300 4	not tested	210 4

*Data not available due to data logger failure

For each substance, two test runs were conducted in each dryer. During the first run, the suspensions were sprayed directly into the empty process chambers. For the second one, a receiver (dry raw material of the respective test substance) was introduced at the beginning of the process to improve the startup process,[43] which allowed to form a fluidized bed prior to spraying. A third set of test runs was conducted on the Glatt Pro-Cell LabSystem using 4 wt% Mowiol© 40-88 as a binder in order to facilitate granule formation and to study the effect on the formation of the fluidized bed.

5.4.3.2 Spray dryer

In order to evaluate the suitability for drying small continuous powder flows, preliminary tests were conducted on the B290 mini spray dryer from Büchi (Büchi Labortechnik AG, Flawil, Switzerland) shown in Figure 2. It consists of a two-fluid nozzle atomizer with 1-3 bar atomizing pressure, a glass spray cylinder (diameter 165 mm, length approx. 500 mm) and a glass cyclone (diameter 120 mm) to recuperate dried products from the drying air. Product was collected in glass receptacles. Continuous product discharge could be achieved by adding (for example) a rotary valves or a shifter. As such adaptations are already well-known technical solutions and to keep the test setup as simple as possible, tests were performed using a glass receptacle only. The suspensions

were sprayed in co-current flow with nitrogen as drying medium. The suspension was fed into the nozzle atomizer with a built-in peristaltic pump with a Ø1 mm feed hose.

Figure 2 Büchi mini spray dryer B-290

Spray drying of Lactose with the B290 at low feed concentrations is a well known procedure.[44] However, spray drying of highly viscous suspensions that cannot be processed with the integrated peristaltic feed pump has not been reported. Thus, a syringe pump was used as a feeder instead of the peristaltic pump. Syringes are a simple solution to demonstrate how augmented feed pressure levels, needed for spray drying of highly viscous products, influence the spray drying process. For spray drying of Ibuprofen a standard setup, that is, the integrated peristaltic feed pump was used. The tests with Ibuprofen were conducted using a 20 wt% suspension, 20 wt% expressing the maximum pump-able concentration level using the integrated peristaltic pump. The process parameters are shown in Table 2.

Table 2 Tested parameter range during spray drying

	Lactose (quality Sorbolac)	Ibuprofen
Feed concentration [wt%]	50	20
Feed mode	Syringe (3 g/min)	peristaltic pump (3-6 g/min)
Nozzle atomizer spray gas flow [l/min]	7-10	7-10
Nozzle atomizer spray pressure [bar]	1.8 -2.4	1.8-2
Temperature drying gas in [°C]	110-130	100
Temperature drying gas out [°C]	53-60	Na*
Drying gas flow [m^3/h]	10-28	Na*

*no stable process could be established

5.4.3.3 Spin flash dryer

A small-scale spin flash dryer of type SFD-47 (SPX Flow Technology Denmark A/S, Copenhagen, Denmark) with throughput of 1-20 kg/h dry product (Figure 3) was tested. The main component was a 0.2m wide and 1m high drying chamber equipped with rotating blades. The scheme of the dryer is shown in Figure 3. Dry particles were separated from the exhaust with a cyclone.

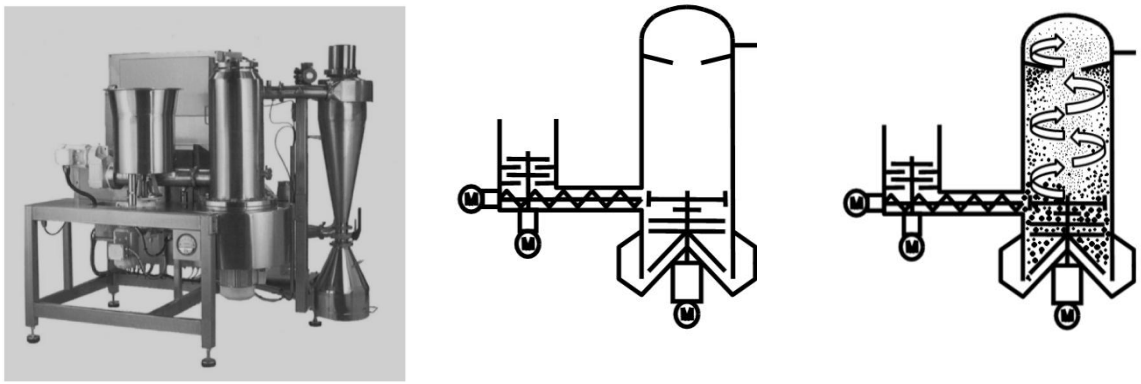


Figure 3 Main components and working principle of a spin flash dryer [45]

60 wt% Ibuprofen and 70 wt% lactose pasty suspensions were dried as shown in Table 3. Their concentration levels were chosen to be high since the feed system is especially designed to handle highly viscous educts.

Table 3 Tested parameter range during spin flash drying

	Lactose (quality Sorbolac)	Ibuprofen
Feed concentration [wt%]	70	60
Feed rate [kg/h]	1-6	1-3
Temperature drying gas in [°C]	80	70
Temperature drying gas out [°C]	48-68	42-65
Drying gas flow [m^3/h]	200-400	200-400
Rotor speed [rpm]	400-1400	400-1400

5.4.3.4 Paddle dryer

The paddle dryer experiments were performed on a Solidaire (Hosokawa Micron bv, Doetinchem, Netherlands), a pilot scale equipment that is generally used for testing before scale-up. Hosokawa's paddle dryer consists of a tube which can be split in a bottom and a top part (Ø0.2m, 1.5m long) with a heated jacket and rotating paddles inside. During testing, rectangular adjustable paddles are used, as shown in Figure 10 below. The maximum paddle speed was 1000 rpm. To remove the evaporated solvent, air was fed to the outlet port and evacuated at the inlet port. The final product was discharged as free falling powder through the outlet port at the bottom end of the tube. The basic process outline is shown in Figure 4.

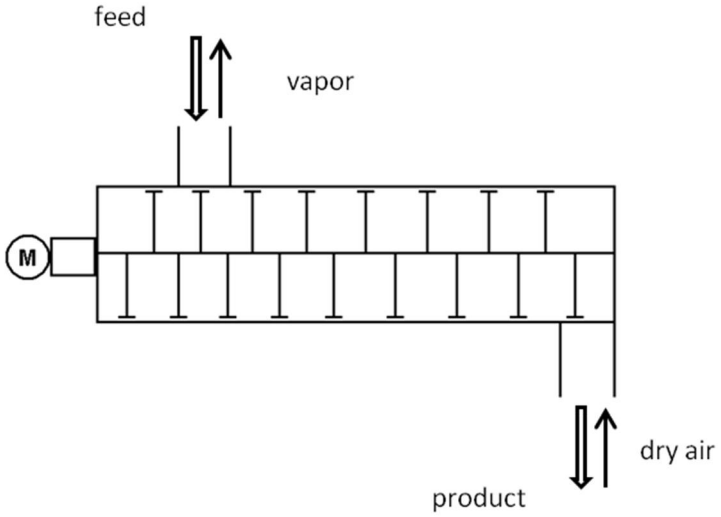


Figure 4 Schematic of the paddle dryer from Hosokawa Micron

Tests were conducted with lactose and Ibuprofen suspensions as shown in Table 4. The feed was supplied to the inlet port manually. Preliminary tests were performed to evaluate the influence of rotation rate and paddle inclination. The effect of the paddle inclination on the achievable residual moisture content was evaluated. In addition, the residence time distribution was evaluated using iron oxide as a colorant to track the material distribution. These tests were conducted feeding white Ibuprofen and red Ibuprofen-iron-oxide suspensions to the paddle dryer in alternating 10 minute intervals.

Table 4 Tested parameter range during paddle drying

	Lactose (quality Sorbolac)	Ibuprofen
Feed concentration [wt%]	60	60
Feed rate [kg/h]	0.3-1	0.2-1
Tube temperature [°C]	80	65
Rotation speed [rpm]	400-800	600-800

5.4.3.5 Extruder

The equipment used in the experiments was a ZSK18MC (Coperion GmbH, Stuttgart, Deutschland), as depicted in Figure 5.

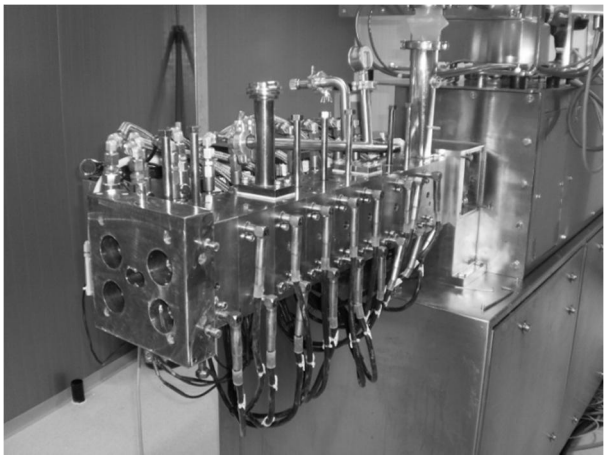


Figure 5 Extruder ZSK18MC from Coperion

The ZSK18MC is a classic hot-melt extruder with two self-cleaning intertwining 18 mm screws (Do/Di=1.55) rotating in eleven individually-heated housing blocks. Housing block 8 had an opening for a vacuum dome and housing block 4 had an additional opening that allowed an airstream to enter or leave the apparatus. The double screw prevents stagnation areas within the extruder and ensures a relatively narrow residence time distribution.[46] Three different screw configurations were tested as shown in Figure 6 to Figure 8.

Each screw contained one left-pitch element that created a fully-filled element (plug) separating the feed section from the vented drying section (in double-screw extruders that are feed-starved, elements are typically not fully filled). To maintain air circulation in the vented zone, high-pitch conveying elements near the left kneading block were used. As such material flux increases after the kneading block. This causes the screw to be only partially filled, allowing the air to pass in the vented area. Screw configuration 1 had one left and one right kneading element at the end of the screw to seal the vented

area near the output. Screw configuration 2 had no kneading elements, leaving the vented area near the output open. Screw configuration 3 had one left kneading element at the end to separate the vented area from the output. The final block either had a die plate with die openings of varying sizes (Ø 1 or Ø2 mm) or was left open.

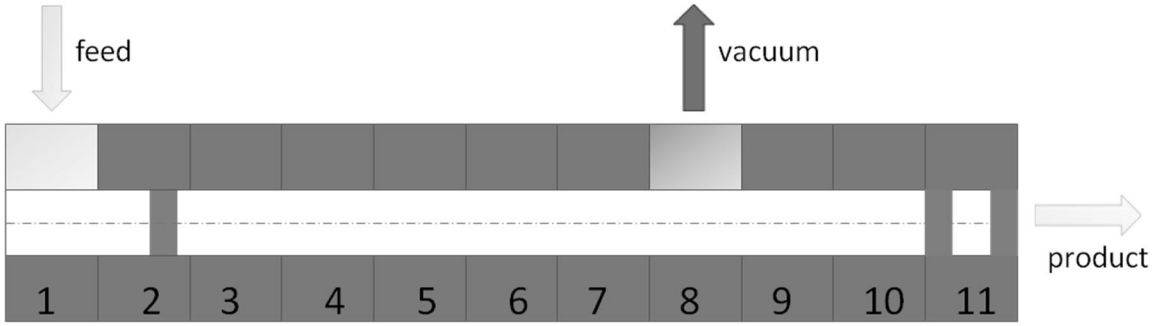


Figure 6 Housing blocks and selected screw elements for screw configuration 1 with a sealed end used for vacuum drying and counter- or co-current drying. Flow streams are indicated for vacuum drying

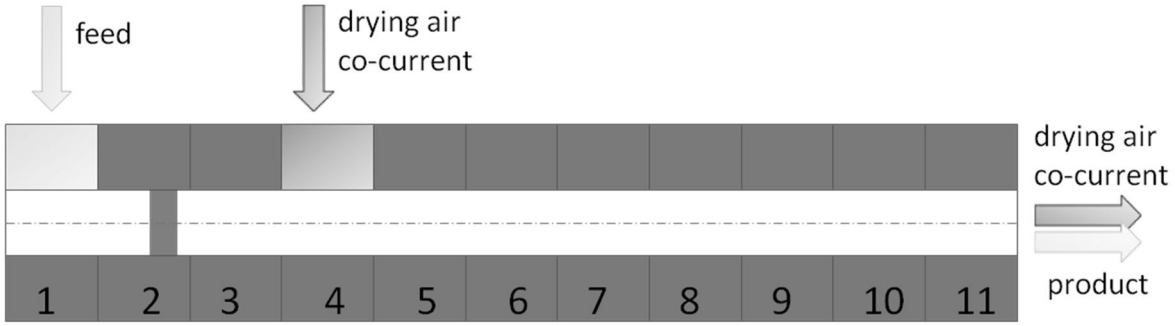


Figure 7 Housing blocks and selected screw elements for screw configuration 2 with an open end used for counter- or co-current drying. Flow streams are indicated for co-current drying

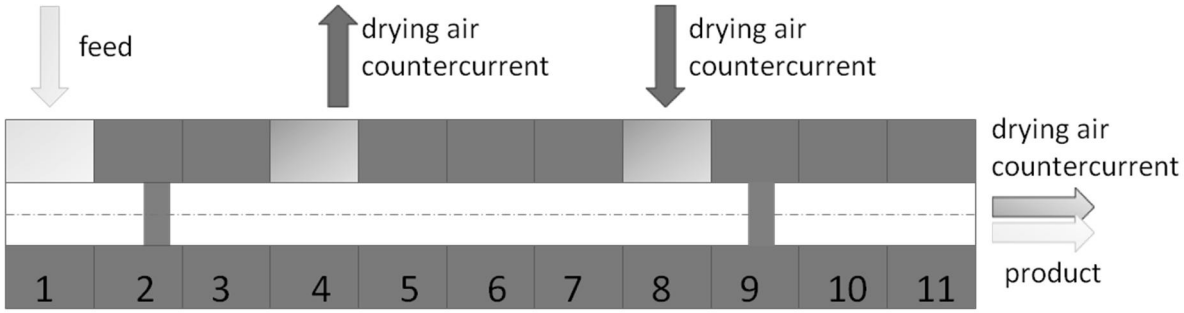


Figure 8 Housing blocks and selected screw elements for screw configuration 3 with a clogged end used for counter- or co-current drying. Flow streams are indicated for countercurrent drying

Three sets of experiments were carried out:

- drying with counter-current airflow,
- drying with co-current airflow and
- drying under vacuum

For counter-current drying, hot air was fed into housing block 8 and removed in block 4 (as indicated in Figure 8). Tests were performed using all three screw and die plate configurations (Ø1 mm holes/ Ø2 mm holes/ no die plate). For co-current drying, hot air was introduced into housing block 4 and removed together with the extruded product (as indicated in Figure 7). In addition, experiments were performed with housing block 8 open to create an additional air outlet. All three screw and die plate configurations were tested. For vacuum drying, a vacuum system was mounted above the extruder screws in housing block 8. Housing block 4 was kept closed (as indicated in Figure 6). Tests were performed for screw configuration 1 and two die plate configurations (Ø1 mm holes/ Ø2 mm holes).

All tests were performed with Ibuprofen suspension only. To study process performance with other substances, additional tests with a lactose suspension were conducted with counter-current drying, with screw configuration 1 and no die plate as shown in Table 5. During all trials, the housing blocks temperatures were adjusted individually.

Table 5 Tested parameter range during extrusion drying

	Lactose (quality Granulac)	Ibuprofen
Feed concentration [wt%]	70	50
Feed rate [kg/h]	0.1-0.7	0.1-0.7
Temperature of housing blocks [°C]	30-80	30-65
Temperature drying gas in [°C]	50	50
Drying gas flow [m^3/h]	9-15	9-15
Vacuum pressure [mbar]	not tested	0-200
Rotation speed [rpm]	50-80	50-80
Tested screw configurations	1	1,2,3
Tested die plate configurations	no die plate	Ø1 mm holes/ Ø2 mm holes/ no die plate

5.5 Results

5.5.1 Fluidized bed spray dryers

One of the important issues is the limitation of the atomizer's spray nozzle with regard to high-viscosity suspensions. Typical suspension viscosities for the DMR two-fluid nozzle atomizer are around 1.5–2.0 mPas. Handling of suspensions with higher viscosities requires a nozzle of a different design [47],[48] or a rotary atomizer. However, since liquids with high viscosity and surface tension are generally difficult to atomize into fine droplets,[49],[50] such a setup may result in irregular droplet formation due to possible accumulation of high-viscosity agglomerates in the pressure nozzle's orifice.[22] The Glatt spray nozzle atomizer had similar restrictions with regard to the educts concentration (Table 6).

Table 6 Residual moisture and process parameter values for best results obtained during fluidized bed drying

	Lactose (quality Sorbolac)		Ibuprofen	
	DMR	Glatt	DMR	Glat*
Maximum sprayable concentration [wt%]	47	50	18	26
Spray rate [g/min]	15	28	3 – 11	10 – 23
Drying air throughput [m^3N/h]	110	60	80 – 140	50 - 80
Drying air pressure difference [mbar]	5	3	3 – 6	Na†
Drying air inlet temperature [°C]	80	60	45 – 80	50 -70
Exhaust air temperature [°C]	43	27	37 – 40	23 – 30
Product temperature [°C]	48	27	38 – 44	25 - 35
Residual moisture test run #1[wt%]	Na‡	Na‡	Na‡	Na‡
Residual moisture test run #2 [wt%]	0.3	Na‡	Na‡	Na‡
Residual moisture test run #3 [wt%]	not tested	0.2	not tested	0.3
X_{50} test run #1[µm]	Na‡	Na‡	Na‡	Na‡
X_{50} test run #2[µm]	85	Na‡	Na‡	Na‡
X_{50} test run #3[µm]	not tested	382	not tested	460

* screening experiment only

†data not available due to data logger failure

‡ fluidized bed could not be established

Start-up of the drying process without a receiver requires a sprayed material that dries quickly, as the free path before collision with a wall is very limited. Wet material does lead to accumulation/sticking of the particles on the process chamber walls. The effect of material buildup during startup greatly depends on the feed rate and spray pressure of the nozzle atomizer and on the drying kinetics of the dried substances.

In all runs, startup of the process without a receiver resulted in a buildup of material on the process chamber walls, preventing the formation of a fluidized bed. Regarding the influence of the process conditions, it can be noted that the bottom-spray configuration minimized droplet adhesion to the surrounding walls. This is due to the fact that in the bottom-spray configuration the droplets have a higher probability of touching already fluidized particles in contrast to the top-spray configuration where entering droplets may reach the wall easier. Note that both tested systems offer possibilities to implement bottom- as well as top-spray configurations.

A receiver helps to pre-establish a stable fluidized bed, where the sprayed droplets collide with particles in the fluidized bed (and not the wall) and start to form a thin layer on top of the particles. The thin layer dries and causes either an increase in PSD of the existing receiver material, or causes the coated layer to break off, adding fine material to the fluidized bed. As this fine material does not fluidize,[18],[17] the establishment of a stable fluidized bed is difficult. Using a receiver, lactose (quality Sorbolac) was dried successfully with residual moisture content of 0.3 wt% with x_{50} of 85 µm on one of the systems. On the other system, however, no stable fluidized bed was achieved. Only adding a binder to the solution enabled formation of a stable fluidized bed. The obtained residual moisture level was 0.2 wt% with x_{50} of 382 µm. Drying of Ibuprofen with help of receiver material was not successful in the fluidized bed spray dryers. Only after addition of a binder a stable fluidized bed could be established. The obtained residual moisture level was 0.3 wt%. with x_{50} of 460 µm.

During the drying process, process air leaves the chamber through air filters mounted just above the fluidized bed. The filters are periodically flushed via a pressure pulse for cleaning. During our tests, filter cleaning worked well and blockage of the filter never occurred. Note that the back-flow air pulse does not completely remove adhering material but only ensures that enough of the filter area is free for operation.

In a continuous production environment the dry powder needs to be continuously (or periodically) discharged. The DMR system periodically discharges dry material through

a bottom hatch depending on the weight of the fluidized material. Thus, wet particles may be in the discharged material, as the system operates similar to an ideally mixed reactor. The Glatt system product discharge is performed continuously via a zigzag sifter, returning fines into the process chamber, which should results in a narrow granule size distribution. However, since the zigzag sifters separate by particle weight and size,[51] it is also difficult to ensure that only dry granules leave the process chamber (i.e., small and wet granules could also be heavy enough to be separated in the sifting process).

Conclusion for fluidized bed drying

Two fluidized bed spray dryers of different designs were tested. The final moisture content of the obtained granules (Table 5) was very low. The results demonstrated that ensuring a stable fluidized bed is crucial to a stable process. From the Geldart classification theory it is apparent that particles considered in our study, are difficult to fluidize. [18],[17] Thus, in order to create stable fluidized beds with small particles, they must be enlarged via granulation. If the sprayed agglomerates deagglomerate during the drying process, a binder substance must be used, which may create issues with the formulation of the final drug substance. However, the change of the particle size distribution may also improve flow properties, making materials easier to handle (e.g., better flowability, possibility for direct compaction, etc., which may be an additional advantage (i.e., multifunctional process).

In all test cases a receiver was required to establish a stable fluidized bed. However, using a receiver may be disadvantageous because an additional material is introduced in the formulation. Nevertheless, the receiver might be used only to establish stable operation at the startup of the process. In case of a stable product, remaining product of previous campaigns can be used as receiver material in order to avoiding additional material costs or new materials.[3]

Standard fluidized bed dryers always exhibit strong mixing and a statistical particle motion, resulting in a broad residence time distribution. Both tested systems offer the op-

tion of dividing the process chamber. Separating the process chamber in smaller zones would lead to narrower residence time distributions per zone. A clear separation of zones would also allow for additional process steps during the drying procedure e.g., an additional coating step. However, dividing a small process chamber into even smaller parts could interfere with the feed cone of the spray nozzle atomizer. Using a larger process chamber would increase significantly the residence time, especially for a small throughput where a long startup time is required to fill the fluid bed and to run in a stable regime.

Our tests demonstrated that both the DMR and the Glatt system provide numerous real time control parameters,[52] as stated in Table 1 which could be used to adapt the process to various products, thereby ensuring flexibility.
In summary, fluidized bed dryers are widely used in pharmaceutical batch processing. With regard to continuous process setups, improvements in filter cleaning, product ejection and optimization of residence time distribution, respectively control of back mixing are required.

5.5.2 Spray dryer

Spraying of the syringe-fed lactose suspension was possible with the existing nozzle atomizer, only drawback being the large droplet size distribution and a rather wide spray cone. Both effects were influenced by the high pressure applied on the feed syringes. The achieved residual moisture level was 1.7 wt%, as indicated in Table 7. No representative PSD measurement could be obtained due to high variation of feed pressure.

Since spray drying is generally performed with low viscosity solutions and suspensions, spraying of a highly viscous material poses several problems, i.e., clogging of the feed system and the spray nozzle atomizer. With Ibuprofen clogging of the spray nozzle lead to a complete blockage of the process soon after startup.

Table 7 Residual moisture and process parameter values for best results obtained during spray drying

	Lactose (quality Sorbolac)	Ibuprofen
Feed concentration [wt%]	50	20
Feed mode	Syringe (3 g/min)	peristaltic pump (3-6 g/min)
Nozzle atomizer spray gas flow [l/min]	10	7-10
Nozzle atomizer spray pressure [bar]	1.8	1.8-2
Temperature drying gas in [°C]	117	100
Temperature drying gas out [°C]	60	Na*
Drying gas flow [m^3/h]	10	Na*
Residual moisture content [wt%]	1.7	Na*
X_{50} [µm]	Na†	Na*

* blockage of the spray nozzle occurred, no stable process conditions achieved
†no representative PSD obtained due to high variation in feed pressure

During all tests material adhered to both the drying tower and the cyclone walls. In the case of lactose this was due to the spray cone enlargement caused by high pressure, which was required for spraying high-viscosity suspensions. Such a buildup can be expected to be reduced in larger equipment.

Material loss also took place during removal from the drying air in the cyclone. Cyclones with high separation efficiency are very costly, especially for very fine particles. Up to a certain point this issue can be addressed by having smaller cyclones in parallel or in series rather than having only one cyclone with a large diameter. However, recuperation of particles below the micron size range will definitely be problematic.[53],[54]

Conclusion for spray drying

Spray drying is an established process in the pharmaceutical industry. Particle size can easily be controlled via the size of droplets formed in the spray nozzle atomizer. Additionally, particle properties with desirable characteristics (e.g., amorphous forms) can be achieved. However, during our tests atomization of highly viscous products was not possible. Clogging of the spray nozzle strongly depends on the spraying gap of the used nozzle.[22] Although high pressure nozzles might mitigate this problem, forming fine droplets when atomizing high-viscosity products is difficult.[24],[49],[50],[55] Moreover, product loss on the equipment walls or in the cyclone results in yields ranging from 60% to 90%.[56],[57],[58],[59],[25] Moreover, the loss of fines smaller than 1 µm is a significant issue for pharmaceutical production, since material costs can be high.[3]

5.5.3 Spin flash dryer

Drying of lactose produced very dry product as shown in Table 8, with only bound crystal water remaining. The uni-modal particle size distribution of the feed material became bimodal in the final product, with one fraction being fine crystals, same as in the feed, and the other one consisting of spherical agglomerates. Agglomerate formation was caused by the creation of solid bridges due to re-crystallization of initially dissolved material of the saturated liquid phase.

Table 8 Residual moisture and process parameter values for best results obtained during spin flash drying

	Lactose (quality Sorbolac)	Ibuprofen
Feed concentration [wt%]	70	60
Feed rate [kg/h]	3	1
Temperature drying gas in [°C]	80	70
Temperature drying gas out [°C]	68	54
Drying gas flow [m^3/h]	200	400
Rotor speed [rpm]	910	420
Residual moisture content [wt%]	0	0
x_{50} of final product [µm]	40	25

Residual moisture levels were also very low for Ibuprofen. Drying of Ibuprofen produced very good results with regard to the particle size of the final powder. As indicated in Table 8, little change in the particle size distribution occurred.

During startup with Ibuprofen, the feed rate greatly affected the deposit build-up on the process chamber's walls. At high feed rates, a layer of wet cake formed on the process chamber's walls, as shown in Figure 9, but gradually disappeared at reduced feed rates. Once stable process conditions were achieved, this problem disappeared due to the self-cleaning effect of the upward powder stream.

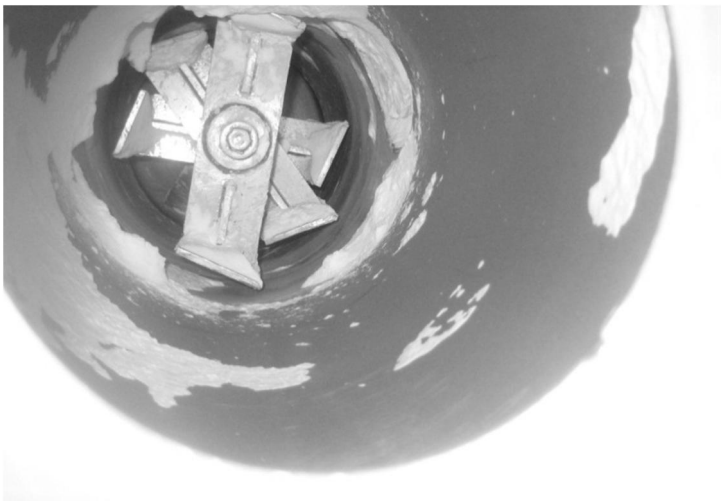


Figure 9 Deposit build-up during start up of Ibuprofen drying

During both lactose and Ibuprofen drying, a small layer of pasty material formed right above the uppermost paddle at the drying chamber wall, where the material is fed into the process chamber. This crust continuously detached and reformed.

Conclusion for spin flash drying

The spin flash drying technology proved to be suitable for processing highly viscous feeds. The screw feeder in combination with de-agglomerating rotating blades produced fine powder, effectively breaking up the agglomerates formed during the drying. The process parameters ensured a stable and fast drying process. The upward powder flow seemed to exhibit a self-cleaning effect depending on the feed rates, i.e., when enough material is involved in the process. Since continuous processing also needs to ensure traceability,[2] a narrow residence time distribution is important. Therefore, measures to prevent crust formation in the lower half of the drying chamber and especially at the feed height are required.

The residual moisture levels were very low. During our tests, the drying air inlet temperature was maintained at a low level to avoid thermal stress of the material. It is important to note that the drying air inlet temperature could be increased to enhance the drying rate but should not be above the materials melting point.

Another issue is the loss of fines due to the separation of the dry particles from the air stream via cyclones. As discussed in the previous chapter, smaller cyclones in parallel could minimize this problem.

5.5.4 Paddle dryer

During lactose drying, a thick uniform crust was formed due to lactose's high solubility in water. The dissolved material re-crystallized and solid bridges were built up. The crust buildup mainly occurred on the tube walls at higher rotating speeds. If rotating speed was reduced, caking also occurred on the rotating axis. The final residual moisture levels were very low at 0.1 wt%. Due to the complete re-crystallization and formation of a uniform crust layer the initial PSD distribution was complete lost in the process. Therefore, measured changes in PSD were considered to be not representative.

In our experiments with Ibuprofen three sections along the dryer axis could be identified. The first section near the feed contained wet pasty material. To transport the feed forward the first section's paddles had to be slightly tilted forward (about 40°). The continuous feeding also constantly moved the material forward. At a certain residual solvent level the material crumbled, leading to the second section, during which agglomerated pasty flakes were formed. Further evaporation and paddle agitation disintegrated the flakes creating a layer of fine powder in the third and last section of the tube. Figure 10 shows a picture of all three sections.

Figure 10 Three sections formed during drying with the paddle dryer. The lower half of the heated tube is shown. Each paddle can be inclined individually. The picture shows drying of Ibuprofen

The length of each section depends on the material-specific drying kinetics, the paddle inclination and the feed flux. The longer the material remains in the dry powder section, the lower the final moisture content. For best drying results such process parameters as the feed rate, the rotation speed, forward transport (via paddle angle) and the jacket temperature had to be adapted to maximize the dry powder section. Best final moisture contents obtained and the corresponding process parameters are shown in Table 9.

Table 9 Residual moisture and process parameter values for best results obtained during paddle drying

	Lactose (quality Sorbolac)	Ibuprofen
Feed concentration [wt%]	60	60
Feed rate [kg/h]	0.3	0.2
Tube temperature [°C]	80	65
Rotation speed [rpm]	600	600
Residual moisture content [wt%]	0.1	0.3
x_{50} of final product [µm]	Na*	58

*PSD not representative due to formation of a solid crust.

During testing with Ibuprofen foaming occurred at rotation rates above 800 rpm, which prevented forward transport of the material and reduced the air flow necessary for drying.

Figure 11 shows the results of an experiment during which a small amount of iron oxide was added to the feed just before stopping the machine. It can be observed that the red-iron-oxide-Ibuprofen mixture was incorporated into a wide area around the feed port. Residence time distribution tests with an alternating Ibuprofen and Ibuprofen-iron-oxide feed with a 10 minutes interval showed that the pasty wet phase was completely exchanged during each interval. That is, after a ten minute feeding of Ibuprofen, no traces of the previously fed Ibuprofen-iron-oxide layer could be identified in the first pasty wet phase. However, in the dry powder section a mixture of both red and the white phase always remained.

Figure 11 Wet pasty phase just past the feed port after adding iron oxide as a colorant to determine the residence time distribution

Conclusion for the paddle dryer

Choosing an optimal feed rate and paddle inclination was necessary to achieve an acceptable final moisture content. Especially, determining the best suitable paddle inclination and form is challenging and product-dependent. For a final GMP design the paddle inclination may have to be set at a fixed angle to ensure cleanability and to reduce the material buildup. Minimizing the forward motion of the paddles by decreasing the axis'

rotational speed was only possible to a certain extent. If the speed was too low, the drying material adhered to the shaft, and at too high rotation rates foaming occurred. As such, for every product optimization of the rotation rate and the paddle inclination may be required.

Since the drying kinetics also depends on air flow, precise control of the air flow through the tube needs to be established. Installing a vacuum for products with low melting points or high solubility at elevated temperatures might be beneficial.

In the paddle dryer, residence time distribution is strongly influenced by the deposit layer in the last section of the dryer tube. Therefore, reducing the amount of material in the deposit layers is crucial. Residence time distribution would improve drastically if (for example) wall clearance between the heated tube and the paddle and the distance between the paddles would be reduced, thereby preventing material buildup.

5.5.5 Extruder

The suitability of extruder-based drying was evaluated. A main result of our work was that the drying air flow has a major impact on the drying process. Several tests were performed to evaluate various screw configurations, die plates and air flow setups. Best results concerning residual moisture and corresponding process parameter values are indicated in Table 10.

Table 10 Residual moisture and process parameter values for best results obtained during extrusion drying

	Lactose (quality Granulac)	Ibuprofen
Feed concentration [wt%]	70	50
Feed rate [kg/h]	0.1	0.3
Temperature of housing blocks [°C]	30-80	30-65
Temperature drying air in [°C]	50	50
Drying air flow rate [m^3/h]	15	15
Vacuum pressure [mbar]	X	200
Rotation speed [rpm]	50	60
Tested screw configuration	1	1
Tested die plate configuration	no die plate	no die plate
Residual moisture content [wt%]	0.4	14
x_{50} of final product [µm]	309	682

Counter-current drying produced flakes with residual moisture of 0.4 wt% for lactose using screw configuration 1 without a die plate. Using the same system configuration for Ibuprofen drying resulted in a residual moisture content of around 14 wt%. An increase in the feed rate led to an increase in the discharged flakes' size. Feeding at the highest rate, 0.7 kg/h, resulted in the discharge of a wet paste.

It was found that it is crucial to adapt the drying air flow rate to the feed rate, the screw geometry and the educts. Minor deviations in the setup led either to product discharge at unintended locations or to process upsets. Thus, while it is feasible to run the process it is difficult to control. For all tested cases drying with screw configurations 2 and 3 with corresponding die plate configurations resulted in higher residual moisture levels than for screw configuration 1.

Co-current drying yielded a wet paste as the final product. Using screw configuration 1 only some dry flakes were discharged with the air stream at the opening in housing block 8. The best results achieved with screw configuration 2 were some dry flakes at the upper rim of the last housing block Screw configuration 3 performed only slightly better.

Vacuum drying of Ibuprofen using a Ø2 mm-hole die plate produced strands (see Figure 12) with 11 wt% residual moisture. Clogging of the die plate occurred during all trials, with larger die openings delaying the effect. The material was sucked into the vacuum system even with the minimum vacuum applied.

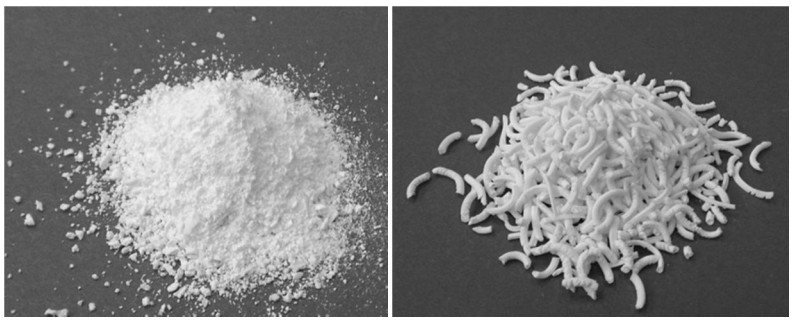


Figure 12 From left to right: Ibuprofen flakes produced with screw configuration 1, extruded Ibuprofen strands produced via vacuum drying

Conclusion for extrusion drying

Extrusion-drying has significant potential for continuous operation. However, the air flow management inside the extruder is the most important issue for an effective drying process. Our tests demonstrate that using the right air flow setup in conjunction with the right screw and die configurations can deliver a good continuous drying process. Pasty products can be easily processed since limitations apply only to low-viscosity products.[46],[41] The self-cleaning effect of the inter-meshing screws [40] is of a major advantage for pharmaceutical production where material buildup is always undesirable. Radl et al. [46] estimate typical residence time distributions for co-rotating twin screw extruders in the order of 2 minutes.[60] Shear stress, which may be problematic for shear-sensible products, had no negative effect on the substances we tested. In order to avoid the significant increase in the product particle size, additional elements to mill the particles before discharge could be installed.

5.6 Comparative Evaluation

In order to systematically compare the tested equipment, 16 relevant criteria were defined and analyzed as shown in Table 11. For reasons of clarity, the analysis presented her is limited to the main findings and conclusions. A sum up of the best results obtained for each tested technology comprising data on achievable residual moisture levels, PSD and corresponding feed throughput and solid concentrations is presented in Table 12 and Table 13.

Table 11 Analyzed process properties

Continuous operation	Handling of viscous pastes	Achievable residual moisture
Throughput at lab scale	Agglomeration/de-agglomeration behavior	Process control
Controlled residence time	Product loss	Overall performance of existing plant
Caking	Product discharge	Development risk
Flexibility	Influence of residual solubility at drying temperature	

First of all, all tested systems were found to be suitable for continuous operation mode. However, for all systems minor modifications and adaptations were necessary to adjust for low throughputs at the lab scale. In that sense, the fluidized-bed spray dryer ap-

peared to be least suitable, as a considerable quantity of material is required to establish a stable fluidized bed. For the tested spray dryer the feed system and the spray nozzle would need to be optimized to adapt for small throughputs. However, atomization of a viscous paste down to very small particles, thus avoiding agglomeration, might be hard to achieve. Scale down of the spin flash dryer would make the process economically more favorable. However, a small throughput is no problem per se for the tested system. The extruder allowed processing of lab-scale throughputs using a special screw design and air flow management.

A uniform residence time is not achieved in a fluidized bed spray dryer, in particular for small throughputs. The flow in the dryer makes residence time control difficult. However, segmentation of the process chamber could improve this characteristic. During spray drying material build-up occurred, which resulted in a rather broad residence time distribution. A wider process chamber could help solve this problem. Similarly, in the spin flash dryer the mix of newly fed product with pre-dried material in the bottom section of the dryer could lead to broader residence time distributions. The paddle dryer showed a broad residence time in the last dry powder section. Furthermore some products may form a continuous solid crust in the drying chamber which remains in the system throughout the whole process. Only the extruder performs very well in this category due to the controlled transport mechanism and the self-cleaning effect.
An issue strongly connected to residence time is caking. In the fluidized bed spray dryer, the cleaning effect of the fluidized particles proved to be sufficient to suppress caking. For the spray drying processes material buildup occurred, yet could be reduced by optimizing the atomizer's parameters and tower diameters. Caking and material buildup were an issues in the spin flash and paddle dryer even though the spin flash dryer also exhibited a self cleaning effect due to the upward directed particle stream. The extruder self-cleaning screws minimize or prevented caking.

As for process flexibility, the paddle dryer and the extruder required considerable adaptations/adjustments when switching from one product to another. The paddle dryer's paddle inclination and geometry and the extruder's screw configuration needed to be optimized for each product. All other processes seemed to handle a product change well

or provided enough adjustable parameters to adapt to changing product demands. Only sprayability of high viscous educts posed a restriction for the spray dryer, as well as the fluidized bed spray dryer.

As expected, pasty products cannot be processed with the standardized two-fluid nozzle atomizers.[49] Other systems such as rotary atomized might be needed. In our studies, the test substances had to be diluted prior to atomizing during fluidized bed spray drying and spray drying. No dilution was necessary for spin flash drying, paddle drying and extrusion drying.

Although for all tested technologies the particle size increased during drying the difference in the particle size varied significantly. Granule formation is inherent to fluidized bed spray drying. In consequence, using this technology, particle size increase has to be desire , i.e., an increase in particle size could eliminate the need for a subsequent granulation.[61] Similar to the fluidized bed spray drying, the extruded products showed a significant size growth. However, as mentioned above, this effect might be controlled by introducing additional milling/mixing elements to the screw configuration. Nevertheless, for many pharmaceutical applications agglomeration is undesired and the original particle properties should be maintained and agglomeration is undesirable. In such cases fluidized bed spray drying, as well as drying with an extruder, require subsequent milling. Formation of agglomerates due to re-crystallization effects also occurred during spin flash drying. To address this problem, rotor impact could be used as process control parameter. Spray drying also offers a means of controlling agglomeration during the drying process by adapting the spray parameters. For the paddle dryer the uncontrolled formation of one continuous solid layer for products that are prone to re-crystallization e.g., for lactose is unfavorable, as the milling of projecting material by the dryer paddles cannot be regulated without influencing the drying process itself.

Table 12 Best results obtained for lactose

		Reference (quality Sorbolac/ Granulac)	Fluidized bed dryer (DMR) (quality Sorbolac)	Fluidized bed dryer (Glatt) (quality Sorbolac)	Spray dryer (quality Sorbolac)	Spin flash dryer (quality Sorbo-lac)	Paddle dryer (quality Sor-bolac)	Extruder (quality Gran-ulac)
Residual moisture [wt%]			0.3	0.2	1.7	0	0.1	0.4
PSD [µm]	X_{10}	1/ 6	43	220	Na†	8	Na†	71
	X_{50}	8/ 34	85	382	Na†	40	Na†	309
	X_{90}	18/ 100	161	575	Na†	155	Na†	1416
Throughput [kg/h]			0.9	1.7	0.18	3	0.3	0.1
Solid content feed [wt%]			47	50	50	70	60	70

*no representative PSD obtained due to high variation in feed pressure

† no representative PSD obtained due to formation of a solid crust

Table 13 Best results obtained for Ibuprofen

		Reference	Fluidized bed dryer (DMR) (no binder)	Fluidized bed dryer (Glatt) (binder added)	Spray dryer	Spin flash dryer	Paddle dryer	Extruder
Residual moisture [wt%]			Na*	0.3	Na†	0	0.3	14
PSD [µm]	X10	13	Na*	337	Na†	2	33	249
	X_{50}	34	Na*	460	Na†	25	58	682
	X90	73	Na*	1020	Na†	56	103	1348
Throughput [kg/h]			0.18-0.66	0.6-1.4	0.18-0.36	1	0.2	0.3
Solid content feed [wt%]			18	26	20	60	60	50

*fluidized bed could not be established

† blockage of the spray nozzle occurred, no stable process conditions achieved

One more important factor was product loss. The separation of powder from an air stream caused significant product loss in the cyclones and filters. This is a general problem for technologies that involve air streams as a transport medium. For spray drying yields as low as 60% are common for small-scale processes with short intervals between product changes.[56],[57],[58],[59],[25] In the paddle dryer product loss to the drying air stream is only a minor problem that could be overcome with a corrected air flow management. Product loss is no issue for the extruder due to the controlled transport. Discharge efficiency is strongly linked to material loss. As previously mentioned, using cyclones resulted in the loss of fines as observed during spray and spin flash dryer trials. The additional zigzag sifter in the Glatt fluidized bed dryer successfully fed fines back into the process chamber. As for product discharge, no problems were encountered with the paddle dryer or the extruder.

Elevated residual solubility caused by high drying temperatures was an issue during the tests involving lactose. However, the effects of solvation and re-crystallization were diminished in processes that used nozzle atomizers or agitators to create small droplet sizes with high surface areas, thereby allowing fast drying.

Obtainable final residual moisture levels were very low for fluidized bed spray drying and spin flash drying. Residual moisture levels were only slightly higher for spray-dried products. Also paddle drying resulted in low residual moisture levels due to elevated residence times in the dryer tube. During our trials extrusion products had the highest residual moisture content.

Process control on the extruder was demanding, as already minor adjustments of the process settings had a large impact on the air flow through the system. Airflow control, however, is the crucial element when drying with an extruder. Therefore finding the optimal process parameters was challenging. The paddle dryer offers few adjustable parameters but once optimized the process proved to be stable and robust. Spray drying and spin flash drying are very robust processes also offering a set of adjustable process parameters for control. The fluidized bed dryer had many adjustable process parameters that could be adapted to the changing process conditions. How-

ever, this increased flexibility made it difficult to establish optimal operating conditions and the system had to be adjusted several times during processing.

The last two criteria are strongly connected: the overall performance and the remaining development risk in order to obtaining equipment fit for pharmaceutical production. The performance of the two tested fluidized bed dryers was good. Nevertheless, further research is required to optimize the residence time distribution and the air filter system. Spray dryers can be bought off the shelf, and adaptations with integrated fluidized beds are already available for the pharmaceutical industry. For the spin flash dryer improvements are needed to handle the material buildup at the feed inlet of the process chamber. Otherwise operation was stable and the remaining development risk is considered low. The paddle dryer, existing at pilot-scale only, requires some basic design-related technical adjustments. Adaptations concerning the paddle geometry are necessary but should not be pose much of a challenge. Likewise, the extruder and its screw configuration need improvements (e.g., correct air stream).

5.7 Conclusion

Five continuous small-scale drying technologies were investigated. Two organic substances (one soluble, the other one only sparingly soluble) widely used in the pharmaceutical industry were dried. Although there are many small-scale continuous drying technologies on the market, all of them except extruders pose major challenges when handling very small material flows (e.g., residence time above reasonable levels).

Further design improvements were recommended for all of the tested equipment. Anhydro SPX's spin flash dryer had the fewest design issues, followed by spray drying and extruder drying. Spray drying is an established technology in the pharmaceutical industry and seems to be a good alternative to spin flash drying. Its only disadvantages are relatively low yields and the low required viscosity of material for atomization. Extruder drying has great potential for pharmaceutical production, particularly since solvent evaporation, mixing and melting can be accomplished using the

same equipment. However, optimizing process streams and screw layout require extensive research and development work. For fluidized bed dryers residence time control offers room for improvement.

The results of this evaluation are based on drying behavior of 2 representative substances. All drying tests were performed in order to get an overall impression of the equipments' limitations for small-throughput drying. For detailed analyses of each small-scale technology further research will be done.

5.8 Acknowledgements

We acknowledge the support of Andreas Eitzlmayr, Daniel Treffer, Michael Piller, Mario Hainschitz, Markus Gamsriegler and Daniel Kaiser of the RCPE. Furthermore, we want to thank VARTA Micro Innovation GmbH for granting us access to their SEM equipment and Meggle AG for donating lactose. We also thank Novartis Pharma AG Basel for the financial support.

5.9 Declaration of interest

The authors report no declarations of interest.

5.10 References

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6. Summary and Outlook

6.1 Summary of Major Findings and Conclusions

Chapters 2 to 4 address the topic of solid liquid-separation in the field of pharmaceutical manufacturing.

Providing a sound basis for subsequent validation of process equipment, chapter 2 is dedicated to the characterization of representative model systems as surrogate for difficult to handle API substances. The results are:

- Implementation of a cake formation test setup in compliance with VDI 2762-2 [65] and advanced experimental evaluation according to Tichy [66]
- Proof of applicability of DLVO theory on model systems comprising organic particles.
- Characterization of model systems. Thorough initial characterization and evaluation of significant substance depending parameters assured comparability to industrial systems.

Chapter 3 describes the selected dynamic cross-flow filtration device and its operational behavior in continuous operation mode. The findings are:

- Aptitude of the equipment to handle process streams and concentrations in accordance with the intended design space was proven.
- Hypotheses, clarifying mechanisms of concentration layer buildup, were developed and validated to explain observed filtration characteristics.
- A simple one-parameter model was developed to allow prediction of filtration performance for any given feed stream.

- It could be shown that one simple pre-test suffices to define the one free material dependent parameter needed for the developed linear one-parameter model.

The very stable operation performance of the tested cross-flow filtration equipment allows constant and easy to predict solid-liquid separation over a wide range of throughputs and slurry concentrations. Aptitude to process a variety of materials could also be shown. The exhibited high flexibility assures ease of implementation for a multitude of different products or champagnes and the constant separation behavior is a big asset for 24hours continuous manufacturing. As one single pre-test suffices to allow full prediction of filtration behavior, process integration is largely simplified. Knowledge of underlying effects concerning concentration polarization layer buildup allow effective design improvements to meet good manufacturing practice (GMP) standards without disturbing the characteristic linear filtration behavior.

Chapter 5 shows alternative operation strategies to enhance filtration performance of the selected cross-flow filtration device. The findings are:

- Evaluation of technical means to enhance filtration performance of the selected cross-flow filtration device.

- Development of an alternative operation strategy, enabling increased permeate flow and in consequence higher concentration factors.

- Comparative evaluation of three operation strategies, two allowing full continuous operation, one for quasi-continuous operation mode.

Increase of process efficiency, in terms of higher concentration factors, reduces the need of additional equipment, either for parallelization or subsequent process equipment. Thus, not only the number of possible sources of errors as well as complexity of the required control system but also manufacturing costs can largely be reduced. Both vacuum enhanced and pulsating operation mode offer increased permeate flow rates. Both operation strategies can easily be realized with the existing equipment, also combinations are conceivable. Only adequate measurement equip-

ment and control strategies for e.g., vacuum level control, have to be thought of to allow fully automated continuous production.

Chapter 4 encompasses analyses on the field of continuous small scale drying of pre-concentrated slurries. Two fluidized bed spray dryers, a spin flash dryer, a mini spray dryer, a paddle dryer and an extruder were evaluated concerning their potential applicability for pharmaceutical production. The findings are:

- Identification of technologies capable of processing selected model systems within the given design space.
- Experimental evaluation of five selected technologies to assess strengths and weaknesses of each technology.
- Deduction of points of improvements for each technology in order to achieve compliance with good manufacturing standards.
- Comparative evaluation of the tested equipment to establish a sound decision bases for further design processes.

It could be shown that a plentitude of equipment is available on the market to achieve thermal solid-liquid separation, even for small throughputs and highly concentrated slurries. However, all of them require further design improvements to comply with GMP standards. The tested spin flash dryer exhibited the least design issues. Implementation of methods to prevent crust formation would make it an ideal choice. Also traditional, established methods such as spray drying showed significant potential, given that issues with atomizer design for highly viscous slurries are solved. Also alternative approaches such as extruder drying are very promising. Design efforts to optimize process streams and screw layout would enable not only drying but also mixing and melting in one equipment, resulting in a very compact, multifunctional process equipment.

6.2 Outlook

Within the pharmaceutical manufacturing community continuous manufacturing is in the center of attention. Implementation of full continuous manufacturing lines is within reach, equipment apt to handle the challenges imposed by the pharmaceutical environment is already far advanced in the developing process. The analyzed dynamic cross-flow filtration device proved to be an optimal choice as follow up step to, e.g. continuous crystallization. As up to now, the device was used for pre-trials and lab tests only, equipment design needs adaptations to reach GMP standards. Exemplary adaptations are prevention of dead zones or improvements on material quality especially for product contacting materials. In the course of this redesign phase, ease of integration of multiple filters should be assured. Depending on the solid-liquid separation task at hand, and the chosen operation mode, as described in chapter 0, multiple devices will have to be implemented in series or parallel. As mother liquid exchange is frequently needed to avoid precipitation or crystallization, suitable means to add wash agent to the filtrated product have to be thought of. In the course of this work, first solutions have been provided; further development to assure simple integration between multiple filtration steps should be considered. Plug and play solutions to maximize flexibility in process layout are most desirable for washing as well as for the filtration equipment. PAT tools to measure process streams especially for small volume streams have already been implemented, however further research is needed to allow direct measurement of highly concentrated retentate slurry.

Design improvements to reach GMP standards are also needed for the drying equipment. As in the course of this work, the thermal drying step was intended as follow up step to mechanical solid-liquid separation, additional challenges arise concerning feeding of highly concentrated slurry. Options including pneumatic and gravimetric feeding have been tested. Solutions meeting industrial standards to connect multiple manufacturing steps have yet to be implemented.

Both, the mechanical- as well as the thermal separation process, have been analyzed to provide profound understanding of process parameters, parameter interactions

and impact on final product quality. An overall control strategy needs to be developed in correspondence with a specific product and the associated requirements. Adequate simulation tools would help to simplify this process and allow e.g. simulation of residence time propagation throughout the whole manufacturing line or enable implementation of model predictive control.

7. Publications

J.S. Gursch chapter “Drying” in “An Overview of Pharmaceutical Manufacturing for Solid Dosage Forms,” by S. Sacher, J. G. Khinast in “Continuous Manufacturing of Pharmaceuticals“, John Wiley & Sons, Ltd, submitted 2014.

J.S. Gursch, D. Dujmovic, J.G. Khinast, J. Brozio, M. Krumme, N. Rasenack “Lösungsmitteleinfluss auf das Filtrationsverhalten organischer Feststoffpartikel”, Proceedings of Minisymposium Verfahrenstechnik 2012, Linz

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