Universidade de Lisboa

Faculdade de Farmácia

Continuous Mixing of Pharmaceutical Pellets

Ana Rita Teixeira Martins

Dissertation to obtain the Master of Science Degree in

Pharmaceutical Engineering

Supervisors:

Prof. Dr. José Monteiro Cardoso de Menezes

Dipl.-Ing. Dr. Stephan Sacher

2016

Universidade de Lisboa

Faculdade de Farmácia

Continuous Mixing of Pharmaceutical Pellets

Ana Rita Teixeira Martins

Dissertation to obtain the Master of Science Degree in

Pharmaceutical Engineering

Supervisors:

Prof. Dr. José Monteiro Cardoso de Menezes

Dipl.-Ing. Dr. Stephan Sacher

2016

The experimental work that supports this dissertation was performed at Research Center Pharmaceutical Engineering (Graz, Austria) in the framework of RCPE's project A3.20 "A European Consortium for Continuous Pharmaceutical Manufacturing of Solid Dosage Forms". All the required facilities, equipment and materials for this work's accomplishment were gently provided.

Abstract

Increasing demands on patient safety and reducing manufacturing costs have driven the pharmaceutical industry to adopt a new manufacturing paradigm: Continuous manufacturing. In order to implement it, all batch unit operations must be converted to their continuous equivalent and raw material feeding issues must be resolved. This study is focused on a continuous blender, the unit operation most commonly needed in manufacturing. A homogenized powder mixture is required to produce oral solid dosage forms with minimum active pharmaceutical ingredients (API) content variability, under strict regulatory constraints. More specifically, the mixing performance of the continuous blender will be studied for formulations containing pellets. Pellets produced by hot melt extrusion are a mean to solve solubility issues of many promising APIs.

The main objective of this dissertation is to characterize the flow behavior inside the blender, using impulse stimulus response experiments and subsequent residence time distribution analysis. The effect of operational conditions, particularly material flow rate and the mixer's rotation speed, on parameters like hold-up mass, mean residence time of pellets and shear intensity were studied. Furthermore, the blender mixing performance was assessed using the relative standard deviation as a mixing index.

The main results are as follows: The hold-up mass decreases when increasing the rotation rate and decreasing the feeding rate. At low throughputs, the mean residence time of pellets increased when increasing rotation rate. The opposite effect was observed operating at higher feed rates. The extension of axial mixing and shear intensity increased when blender's velocity increased. No particular trend was observed on them by changing flow rate. A low rotation rate combined with a high feed rate showed the best mixing performance.

Continuous manufacturing can be realized when on-line process analytical technologies (PAT) are available. In this work, efforts were done to implement on-line near-infrared spectroscopy (NIR) to monitor blend homogeneity without satisfactory results. In order to achieve the goal of this thesis, one subsequently used an off-line method.

This work gave insight about how pellets behave in a continuous mixer under different process parameters and what are the better conditions to achieve a homogenous blend.

Keywords:
Continuous mixing; pellets; residence time distribution (RTD); blend homogeneity.

Resumo

A mistura é uma operação unitária sempre presente na indústria farmacêutica. Na produção de formas farmacêuticas sólidas, é necessário incluir vários outros componentes para além da substância ativa. Excipientes como diluentes, aglutinantes, desintegrantes, lubrificantes, entre outros, são adicionados de maneira a melhorar a estabilidade e biodisponibilidade do fármaco, aumentar a aceitabilidade por parte do paciente e atuar como adjuvantes do processo de produção. Precisamente, a mistura é o processo que permite distribuir uniformemente os vários constituintes da formulação através do movimento das partículas ao longo de todo o granel. Trata-se, portanto, de um passo crítico na produção secundária de formas farmacêuticas sólidas, já que em última análise, afeta a uniformidade de dose do medicamento final.

A produção de medicamentos na indústria farmacêutica é geralmente realizada em *batch*, enquanto outras indústrias operam em modo contínuo, como é o caso das indústrias química e alimentar. Num processo contínuo, o rendimento dos diferentes equipamentos estão coordenados de maneira a que não ocorra acumulação de massa dentro do sistema, já que a entrada de matérias-primas se dá à mesma velocidade que a saída do material processado, durante um período de tempo ininterrupto. Nos últimos anos, as autoridades reguladoras do medicamento têm vindo a reconhecer a produção em contínuo como alternativa à produção por lotes e o seu potencial em melhorar a qualidade dos medicamentos. Os custos de produção podem ser reduzidos, já que existe processamento de grandes volumes com equipamento de menores dimensões, poupança de energia, menor interferência dos operadores, aumentando a segurança dos mesmos e reduzindo os riscos de segregação devido ao manuseamento de pós entre as diferentes operações. A produção em contínuo implica menos problemas de *scale-up*, já que o tamanho do lote é definido pelo fator "tempo". Como tal, o mesmo tamanho de equipamento pode ser usado para a fase de desenvolvimento, estudos em escala piloto, ensaios clínicos e para a produção comercial. Mais importante ainda, é a oportunidade de implementação de tecnologias analíticas de processo como sistema de aquisição de dados integrado em todas as operações da linha de produção. Isto permite o controlo de qualidade em tempo real dos intermediários (como por exemplo tamanho dos grânulos ou homogeneidade de mistura) e do produto final. Como resultado, é possível

conhecer e controlar as fontes de variabilidade do processo e tomar sobre ele decisões cientificamente fundamentadas.

O presente trabalho é parte integrante de um projeto de desenvolvimento de uma linha de produção de formas farmacêuticas sólidas em contínuo (mais propriamente comprimidos), compreendendo os processos de extrusão, esferonização, mistura e compressão. Posto isto, o objetivo deste trabalho é desenvolver conhecimento sobre o processo de mistura em contínuo envolvido, quando utilizando *pellets* e lactose monohidratada.

No contexto farmacêutico, os *pellets* podem ser definidos como pequenas partículas, aproximadamente esféricas, com diâmetro compreendido entre 0.5 e 1.5 mm, produzidas pela aglomeração de pós finos. Caracterizam-se especialmente pelas ótimas propriedades de escoamento, associadas à desvantagem de facilitada segregação. A utilização de comprimidos contendo *pellets* prende-se com a oportunidade de aumentar a biodisponibilidade e permitir a libertação modificada do fármaco, ou a administração de fármacos incompatíveis. Neste sistema, a substância ativa pode encontrar-se no núcleo dos *pellets* ou no seu revestimento.

De acordo com o conhecimento atingido neste trabalho, o processo de mistura contínua usando *pellets* farmacêuticos ainda não foi reportado na literatura. Quanto ao processo em si, mereceu a atenção de diversos grupos de investigação na última década, que têm vindo a estudar o efeito de variáveis de processo (caudal de entrada, velocidade de rotação das pás, número e orientação das pás, inclinação do misturador) no comportamento de pós durante o seu fluxo no interior do misturador. No entanto, a relação entre a eficiência do misturador e as propriedades dos pós utilizados, como por exemplo o tamanho, forma, densidade ou a coesão entre diferentes tipos de partículas não foi tão extensivamente analisado.

A presente tese divide-se em dois grandes objetivos. Primeiramente, caracterizar o comportamento dos *pellets* no interior do misturador sob diferentes caudais de entrada e diferentes velocidades de rotação das lâminas, usando distribuições dos tempos de residência. Pretende-se analisar as variações nos parâmetros volume de retenção, tempo de residência médio dos *pellets* e lactose e número de passagens das lâminas. Adicionalmente, a homogeneidade da mistura obtida será analisada igualmente sob a variação dos mesmas condições de processo, fazendo o misturador funcionar continuamente durante dez minutos.

Será aplicado o índice de homogeneidade geralmente utilizado na indústria farmacêutica para avaliação da qualidade de misturas, o desvio padrão relativo à média.

A monitorização de um processo de mistura em contínuo é realizado calculando a concentração do componente de interesse na mistura (geralmente a substância ativa e neste caso os *pellets*), quando esta forma um fluxo de material à saída do equipamento.

O primeiro grupo de experiências levadas a cabo focaram-se no desenvolvimento de um método *on-line* usando espectroscopia de Infravermelho Próximo (NIR) para monitorizar o processo de mistura. Esta técnica foi já implementada com sucesso no estudo de processos de mistura em contínuo. No entanto, aqui a espectroscopia NIR foi abandonada na fase de desenvolvimento de um modelo de calibração, cujo objetivo seria prever a concentração de *pellets* à saída do misturador. A aquisição de espectros NIR das amostras de calibração foi realizada sob condições o mais semelhante possível às condições de aquisição de espectros no processo de mistura em contínuo e foram aplicados pré-processamentos espectrais adequados. No entanto, os modelos PLS (*partial least squares*) obtidos apresentaram elevados erros de previsão. Vários fatores podem ter levado à aquisição errónea de espectros. Em primeiro lugar, nas amostras de calibração, os *pellets* surgiram completamente cobertos por lactose. Para além disso, é sabido que o movimento das partículas das amostras influencia as medidas do NIR, ao contrário de amostras analisadas estaticamente. Em trabalhos posteriores, sugere-se a utilização de *pellets* contendo no seu interior uma substância ativa que apresente um pico de absorvância característico na região do infravermelho próximo.

Consequentemente, os tempos de residência e a homogeneidade da mistura foram estudados usado uma técnica *off-line* de análise do tamanho de partícula para medir a concentração de *pellets* em amostras recolhidas manualmente à saída do misturador.

Relativamente à caracterização do comportamento do fluxo de material no interior do misturador, os resultados obtidos resumem-se a seguir. O volume de retenção de material no interior do misturador diminuiu quando aumentou a velocidade de rotação das pás, e aumentou à medida que o caudal de entrada aumentou. Usando um caudal de entrada de lactose de 2 kg/h, o tempo de residência médio dos *pellets* aumentou à medida que a velocidade de rotação aumentou. Nestas condições, foi visto que predominam forças centrífugas dentro do equipamento. Logo, o fluxo à entrada não tem força suficiente para empurrar os *pellets* ao longo da câmara. Deste modo, passaram mais tempo a sofrer mistura

na direção radial, em vez de se moveram na direção axial, resultando num maior tempo de residência. A existência de *back mixing* pode ser questionada e também explicaria o elevado tempo de residência dos *pellets* nas condições experimentais referidas. A extensão da mistura na direção axial e o número de passagens das lâminas sofridos pelos *pellets* (usado como medida da intensidade de corte aplicada) aumentou quando a velocidade de rotação das lâminas aumentou. Não se observou nenhuma tendência particular nestes parâmetros ao fazer variar o caudal de entrada.

A velocidade de rotação do misturador foi o parâmetro que mais afetou a homogeneidade da mistura obtida à saída do equipamento. A menor velocidade de rotação testada, correspondente a 100 rpm, revelou a melhor qualidade de mistura, refletido no menor valor do desvio padrão da concentração de *pellets* em cada amostra recolhida, relativo à média. Nesta experiência, a lactose foi alimentada a 8 kg/h e os *pellets* a 3.43 kg/h. Este resultado pode ser justificado por um valor intermédio do tempo de residência dos *pelles* nestas condições. Deste modo, despendem mais tempo no interior do equipamento para sofrer maior número de revoluções juntamente com a lactose, resultando numa melhor homogeneidade. Outra razão para a boa qualidade da mistura resultante é a maior precisão dos equipamentos de alimentação de sólidos quando operam a velocidades mais elevadas.

Em suma, a presente dissertação contribuiu para o conhecimento sobre o comportamento dos *pellets* durante um processo de mistura em contínuo, sob diferentes condições de processo. Proporcionou alguma perceção sobre as melhores condições para atingir uma homogeneidade de mistura aceitável. Não obstante, os resultados e conclusões aqui revelados podem não observar-se usando outro tipo de *pellets*. Num verdadeiro processo de produção de comprimidos, os *pellets* conteriam uma ou mais substâncias ativas e, como resultado, a sua densidade seria diferente. Este fator é suficiente para induzir um comportamento de mistura diferente ou levar a maiores tendências de segregação.

O trabalho experimental que suporta esta dissertação foi realizado na empresa Research Center Pharmaceutical Enginnering (Graz, Áustria) no âmbito do projeto A3.20: *A European Consortium for Continuous Pharmaceutical Manufacturing of Solid Dosage Forms*.

Palavras-chave: Mistura em contínuo; *pellets*; distribuição dos tempos de residência; homogeneidade da mistura.

Acknowledgments

My first gratitude words go to Stephan Sacher and Marcos Llusa, for the opportunity to perform my Master's Thesis in such a well-recognized company and in a great working atmosphere. Especially to Marcos, for all the enlightenments, for tutoring me through my work and for all the helpful tips and advices. A great thank you to Professor José Cardoso de Menezes for having opened this experience door for me and also, for revising my thesis.

I would also thank RCPE's laboratory team for all the technical support.

A distinct thanks to my flat mates Christina and Lena who gave a special taste to my stay in Graz. It was a great pleasure to share the house with you both, thanks for the stories, laughs and sharing.

I have to thank to Joana, Nélio, and Diogo for the time spent together, for their advices and for making me feel more close to our country.

And of course, my friends in Lisbon and especially to my best friends Inês and Susana for being present practically every day.

To Ricardo, my dearest fellow, for the last four years full of joy and love. Thank you for always encouraging me.

To Margarida, for understanding my absence and for the constant friendly brotherhood even at a distance. I wish you the best in life and that one day you'll be a successful woman.

There are no words to express the gratitude to my parents, that supported me financially and made my experience abroad possible; but more importantly for their strength and for always believing in my success. I dedicate you this thesis.

Contents

List of Tables

List of Figures

List of Abbreviations

API	Active pharmaceutical ingredient
AUC	Area under the curve
CSTR	Continuously stirred tank reactor
DIA	Dynamic image analysis
FDA	Food and Drug Administration
ICH	International Conference on Harmonization
LIF	Light induced fluorescence
MCV	Mean centered variance
MRT	Mean residence time
NIRS	Near-infrared spectroscopy
PC	Principal component
PEPT	Positron emission particle tracking
PFR	Piston flow reactor
PLS	Partial least squares regression
PVP	Polyvinylpyrrolidone
RMSEC	Root mean square error of calibration
RMSECV	Root mean square error of cross-validation
RMSEP	Root mean square error of prediction
RPM	Revolutions per minute
RSD	Relative standard deviation
RTD	Residence time distribution
SIMCA	Soft independent modelling of class analogy
SNV	Standard normal variate
VRR	Variance reduction ratio

Chapter 1 – Introduction

Blending is an always-present and essential unit operation in pharmaceutical processes. For instance, when manufacturing a solid dosage form, it is necessary to include several components apart from the active pharmaceutical ingredient (API), such as diluents, binders, disintegrants and lubricants, in order for the final pharmaceutical product to achieve functionality, stability, patient compliance, process aids, among other factors. Powder mixing is the operation for formulation homogenization and to reduce nonuniformities or gradients in bulk's composition. Consequently, it is a critical step in the secondary manufacturing of pharmaceutical solid dosage forms, affecting directly the homogeneity of the powder mixture and thus the dose uniformity of the end product. The art of powder mixing needs a better scientific understanding to achieve the excellence in quality, efficiency and reliability of the product in order to bring a safe treatment to the patient.

The present work is an integral part of RCPE intent of developing a continuous secondary manufacturing line, i.e. for final oral dosage forms production, namely tablets. It will begin with feeding systems of API and other excipients into a hot melt extrusion-spheronization process. Thereafter, the pelletized material will be mixed with the excipients necessary for the tablet compressing process. Hence, the aim of this dissertation is to develop a process understanding of the continuous blending equipment, when using a formulation containing pellets, which will be a crucial element of the aforementioned line for drug product manufacturing. To my knowledge, continuous mixing of pharmaceutical pellets has not been described yet in literature.

More precisely, the two main goals of this dissertation are:

i. To characterize the flow behavior inside the blender, measuring residence time distribution (RTD) and studying the effect of operational conditions (material flow rate and speed of rotor blades) on parameters like hold-up, mean residence time, bulk residence time, mean centered variance and the number of blade passes;
ii. To characterize the blend homogeneity and segregation tendencies using the homogeneity index relative standard deviation (RSD), for assessing the better mixing performance.

1.1. Continuous manufacturing

Batch processing with laboratory testing of samples of final products (e.g. tablets) and intermediates (e.g. pellets) has been typical of pharmaceutical companies' proceedings, while continuous manufacturing has long been adopted by other industries, like the chemical and food ones (McKenzie et al., 2006). The regulatory authorities, mainly the Food and Drug Administration (FDA) in America, have recognized that continuous processing has the potential to improve product quality and are encouraging the pharmaceutical industry to move towards more efficient and consistent processes (Chatterjee, 2012). This change in mindset is highlighted in the ICH Guidelines Q7, Q8 and Q9 and FDA Guideline for Industry – PAT.

In an end-to-end continuous pharmaceutical manufacturing process, different process steps are sequenced to form a continuous production line characterized by no accumulation of mass within the system, since input raw materials are continuously fed into the system and the processed output materials are continuously removed (at the same rate as input of raw materials), during an uninterrupted period of time (Allison et al., 2014).

There are several advantages of continuous manufacturing for the pharmaceutical industry. For instance, it allows: 1) higher production volumes; 2) reduction of waste; 3) increased yield; 4) energy savings; 5) smaller equipment compared to batch processing; 6) less operator interference without manual handling, thus improving safety (Plumb, 2005). Furthermore, continuous production equipment implies fewer scale-up issues, since the size of the production lot is defined by the factor "time"; consequently, the same equipment size can be used for development, pilot studies, clinical trials and for commercial production (Byrn et al., 2015). Continuous manufacturing is enabled by the implementation of process analytical technologies (PAT) as an integrated data acquisition system over all unit operations (FDA, 2004). PAT allows for a real-time quality control of the products being manufactured at different stages of the production line, better process mechanistic understanding (particularly important is to understand the interaction between unit operations and the propagation of changes/disturbances through the system), science-based decision-making and ensuring that sources of process variability are identified and controlled (Chatterjee, 2012; International Conference on Harmonisation, 2009). The latter translates into a higher and more consistent quality of drug final products as well as faster production-

to-market time, since real time release is part of the quality-by-design (QbD) approach (Fonteyne et al., 2015; McKenzie et al., 2006). Additionally, real-time rejection of small quantities of nonconforming product can be performed without sacrificing the entire batch (Byrn et al., 2015). All these benefits ultimately decrease production costs (Schaber et al., 2011). Particularly, continuous mixing allows high production capacity with more compact equipment and less solid handling such as filling and emptying of blenders (potentially reducing undesirable effects like segregation). PAT allows a better control around a well-defined steady state using on-line instrumentation at the outcoming stream, thus not disturbing the bulk during continuous mixing (Muzzio et al., 2004).

A typical continuous manufacturing line for tablet production (the most common form of solid oral dosages) consists of following unit operations and has already been implemented and reported in literature (Ervasti et al., 2015; Simonaho et al., 2016). These authors developed two different continuous setups, namely a direct compression configuration and a line comprising blending, dry granulation by roller compaction, a second blending and a tableting process. In both configurations, different ingredients are continuously added to the production system with feeders operating at a rate which is defined by the composition of the formulation. Powder transfer between unit operations can be performed with the aid of gravity or by conveyors. Albeit it was not performed in any of these two previous configurations, tablets could be also coated in a continuous coater.

In the different options for pharmaceutical secondary manufacturing, schematically illustrated in Figure 1, blending stands out as a crucial and one of the last steps where variance can be introduced, mitigated or managed (Pernenkil, 2008), thus it should be well understood and optimized.

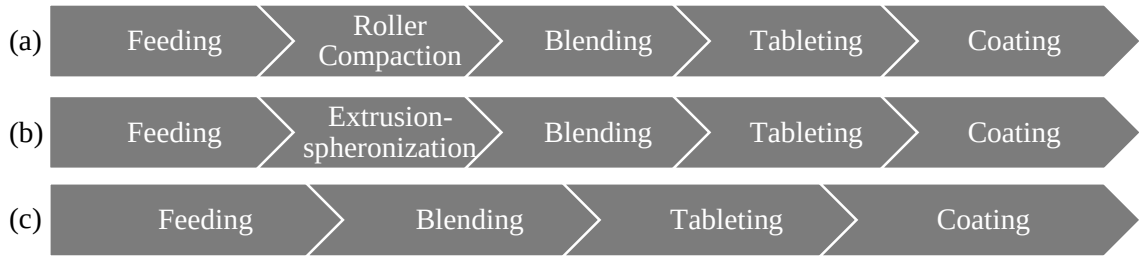


Figure 1: Different continuous manufacturing configurations for tablets production: (a) PROMIS line described in Simonaho et al. (2016). (b) Continuous production line being developed at RCPE's facilities. (c) Direct compression configuration.

1.2. Continuous dry mixing

The role of continuous mixing is to reduce segregation of fluxes that are fed continuously into the system (Gao, Muzzio, & Ierapetritou, 2011). This process can be described as a combination of axial and radial mixings (Williams, 1976), as represented in Figure 2. Axial mixing is the longitudinal particle movement parallel to the passing-through direction and is important in order to smooth out fluctuations introduced by the feeding system. On the other hand, radial mixing occurs at right angles to the passing-through direction and its role is to blend the initially unmixed materials to reach the desired degree of homogeneity (Gericke, 1993; Vanarase & Muzzio, 2011). The material is mixed and the volume of material in the mixer is maintained constant by equal amounts of material being introduced by feeders and removed by axial transport along the system.

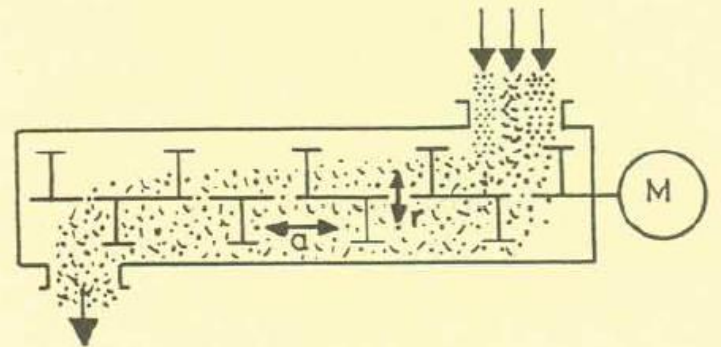


Figure 2: Continuous convective mixing. a = axial dispersion effect, r = radial mixing effect. M = motor. Adapted from Gericke (1993).

Continuous blenders are typically tubular blenders which consist of a horizontal cylinder and a bladed shaft which rotates along its central axis (Figure 2). Powder is fed in one end and the impeller moves the powder to the other end of the chamber and out of the equipment. Blending requires optimization of axial and radial movements of particles in the blender (Gericke, 1993).

The power blending mechanisms in batch systems are also present in continuous systems. For example, convective, diffusive and shear mixing occur in continuous blending systems as well (Pernenkil & Cooney, 2006). Convective mechanism refers to the motion of groups of adjacent particles within the mixture i.e. clumps motion. Diffusive mixing is the random movement of individual particles across slip planes or failure zones and on the freshly exposed surface, to ensure mixing on a fine scale. Shear mixing occurs when internal

blending elements induce shear in particles thereby generating velocity gradients on the powder bed (Lacey, 1954; Poux et al., 1991). All take place during mixing, but they vary in extent with the type of mixer used. Convective mixing predominates in machines utilizing a mixing element moving in a stationary container (Hickey & Ganderton, 2010) just as the blender used in the present study.

It should be emphasized the essential role of continuous powder feeders for the overall performance of the continuous manufacturing line. The tablet API content (and also other ingredients' content) will fluctuate if there is a large variability in the inflow composition, even if the mixer and tablet press would operate perfectly (in the case of the most straightforward example of a continuous direct compression line). Hence it is necessary to ensure that the feed rate of each bulk material is controlled accurately, since powder flow is dependent the on feeder's design (screw type, charging container configuration) and powder cohesion (Engisch & Muzzio, 2012; Hou, Dong, & Yu, 2014).

The throughput of each piece of equipment in a continuous line set-up needs to be coordinated, to avoid material accumulation or running out of it (e.g. keep mass balance). Besides that, it is important to understand the process disturbances and how they are dampened, maintained or even magnified in subsequent unit operations. A key parameter for that is the residence time distribution (RTD) of each piece of equipment (Simonaho et al., 2016). In the batch blending, all the material is inside the blender during the blending process; in contrast, a continuous blender both blends and transports the material, thus there is a certain time or time distribution that describes how long blended material stays inside the mixer. Therefore, RTD with its associated measurements (mean and variance) provide key indexes for flow behavior evaluation (Nauman, 2008).

In the pharmaceutical industry, the acceptance of a good blend is usually based on the relative standard deviation (RSD) of the concentration of the component of interest in the mixture (normally the active pharmaceutical ingredient) (FDA, 2003).

In most cases, the monitoring of a continuous blending is performed at the outlet of the equipment when the blend is forming a powder stream, by measuring the component of interest, which normally is the API (Berthiaux, Marikh, & Gatumel, 2008; Gao et al., 2011; Martínez et al., 2013; Portillo, Ierapetritou, & Muzzio, 2008; Vanarase & Muzzio, 2011).

1.2.1. Studies on continuous powder blending

The earliest work on continuous blending addressed the blender efficiency based on the variance reduction ratio (VRR) which corresponds to the ratio of the variance of the input stream of the blender to that of the output (Beaudry, 1948). The variance reflects the intensity of segregation of the mixture in that stream, thus the VRR (Equation 1) reflects the performance of the blender in reducing this intensity of segregation, and is defined as:

$$VRR = \frac{\sigma_i^2}{\sigma_o^2} \quad \text{(Equation 1)}$$

where σ is the standard deviation of the concentration of the component of interest in the mixture; the subscript i is for input and o for output. Although this homogeneity index is not going to be applied in this work, it´s possible to understand from Equation 1 that a higher VRR corresponds to a better mixing performance of the blender, since it represents a powder with low variance at the output.

The research on continuous mixing applied to pharmaceutical industry is currently a widely studied area and most of the research has been performed in the last decade. The following paragraphs summarize the main findings reported in the continuous pharmaceutical mixing literature.

Much of the initial research on continuous blending of powders applied principles of continuous liquid mixing and the design principles based on response-stimulus experiments (Pernenkil & Cooney, 2006).

The use of non-dimensional numbers such as the Froude number has been applied to the study of powder continuous blenders. The mixing process is characterized by the Froude number, which describes the ratio of centrifugal force to gravity that act over the ingredients in the mixer (Gericke, 1993; Ottino & Khakhar, 2000). The Froude number (Fr) is calculated using the following equation:

$$Fr = \frac{R\omega^2}{g} \quad \text{(Equation 2)}$$

where R corresponds to the radius of the impeller (m), ω is the angular velocity of the impeller (rad/s) and g is gravity (m/s^2). By calculating Fr, mixers can be classified in three categories according to their mixing methods (Berthiaux et al., 2008; Ervasti et al., 2015; Gericke, 1993; Marikh et al., 2005): in mixers with a Froude number below 1, gravitational

forces are predominant and mixing is achieved by displacement and diffusion of particles; a Froude number slightly above 1 indicates fluidized motion of material inside the blender, there is a reduced friction between the particles and a fast mixing effect is achieved with low energy input; a Froude number considerably above 1 means that centrifugal forces are predominant and there is more attrition of the materials that flow inside the blender.

The powders described in the continuous blending early stage reported literature were not pharmaceutical materials. Some examples are: mixtures of sand and salt (Williams & Rahman, 1972), mixtures of sand and sugar (Harwood et al., 1975), non-pharmaceutical pellets (Sudah et al., 2002), chocolate mixture particles (Ziegler & Aguilar, 2003). From this list, the only particulate mixture that is physically similar to the one used in this study is a mix of semolina and couscous (Marikh et al., 2005) that exhibit some tendency to segregate since they have different particle sizes and are free flowing particles.

Engineering aspects of continuous dry powder mixing have been quite extensively studied, namely the influence of different process parameters. However, so far, studies analyzing the effect of material parameters, as particle size, shape, density and cohesion are fewer.

The study of continuous blending processes using pharmaceutical powders has been assessed only in recent years and until the review of Pernenkil & Cooney (2006) pharmaceutical mixes have not been reported in continuous blenders.

Table 1 resumes some of the most important work carried out in the field of continuous pharmaceutical blending.

Table 1: Significant conclusions from investigations on continuous pharmaceutical blending reported in the literature and corresponding powder mixtures, equipments and monitoring techniques handled. References are ordered by date. Abbreviations: APAP – acetaminophen; OTC – over-the-counter drug; MCC – Micro-crystalline cellulose; HPMC – hydroxypropyl methylcellulose; MgSt – magnesium stearate; NIRS – Near infrared spectroscopy; LIF – light induced fluorescence; PEPT – Positron Emission Particle Tracking.

Powder mixture components	Blender type	Monitoring technique	Objectives	Key conclusions	References
Caffeine APAP Lactose MCC MgSt	Zigzag continuous blender and double helical ribbon blender	NIRS LIF	Pulse stimulus response experiments and RTD analysis to study the effect of rotation rate and size, shape and cohesion of powders in flow behavior and final homogeneity.	Increase in particle size and decrease in cohesive forces increased the axial dispersion coefficient and the blender performance.	(Pernenkil, 2008)
Lactose APAP	GEA mixer (model not disclosed)	Off-line NIRS	Study the effects of mixer angle, agitation speed, number and angle of blades in the residence time and blend homogeneity using pulse injection experiments.	The upward processing angle and lower impeller rotation rate (16 rpm) resulted in better homogeneity, corresponding to a longer residence time inside the blender.	(Portillo et al., 2008)
Formulation of a OTC drug containing 3 actives for a total of 9 ingredients	Gericke GCM 500®	Sampling on conveyor belt + HPLC	Compare the flow behavior and blend homogeneity of 2 types of stirrer under different rotational speeds and feeding rates, using VRR and industrial standards (coefficient of variation).	The mobile A gave better mixtures than mobile B. An excessive rotational speed led to worse quality blends.	(Berthiaux et al., 2008; Marikh, et al., 2008)
Edible Lactose Fast Flo Lactose	GEA mixer (model not disclosed)	PEPT	Examine the effect of impeller rotation rate, flow rate and powder cohesion on the particle trajectory, dispersive axial transport coefficient and residence time.	Particles move along the axial length at the same pace. No dead zones exist. Residence time showed an exponential dependence on axial dispersion.	(Portillo et al., 2010)
MCC Avicel PH102	Gericke GCM 250®	On-line NIRS	Real-time determination of API concentration on the outcoming	This was the first application of NIRS and multivariate data	(Vanarase et al., 2010)

Micronized APAP, Silicon dioxide MgSt			blends, using partial least squares (PLS) calibration models.	analysis for real time monitoring of a continuous pharmaceutical mixing process.	
APAP MCC Avicel PH200	Gericke GCM 250®	Off-line NIRS	Characterize the effects of 2 feed rates, 2 blade configurations and 4 blade speeds on mixing performance based on a RTD-RSD correlation.	Moderate blade speed (100–160 rpm) and alternate blade configuration facilitate mixing. Change of feed rate showed no significant influence to the output variance.	(Gao et al., 2011)
APAP MCC Avicel PH200	Gericke GCM 250®	Off-line NIRS	Study the mixing performance and flow behavior using RTD, mean residence time, mean centered variance, hold-up, number of blade passes and RSD measurements, under different feed rates, rotation rates and blade configurations.	Intermediate rotation rates showed the best mixing homogeneity, corresponding to low mean residence times. This was the most significant process parameter affecting mixing performance.	(Vanarase & Muzzio, 2011)
Active ingredient Granules MgSt	Hosokawa Micron Modulomix®	In-line NIRS	Development of a PLS model for the in-line API quantification at the blender outlet, under different flow rates and rotation rates. Study which parameters interfere with NIR results' accuracy.	The PLS model showed to be sensitive to variations on feeding rate (less material flowing over the NIR probe). Lower rotation rates revealed better blends and a more stable powder presentation to the NIR probe.	(Martínez et al., 2013)

In general, the effects of the operating factors are complicated and difficult to be predicted. Operations empirically optimized in one mixer may not be directly utilized in other mixers. For example, some studies suggested that better mixing occurs when RTD is broader (Marikh et al., 2006), while inverse findings were reported on Portillo et al. (2008), in which the most dispersed RTD corresponded to the worst mixing.

1.2.2. Monitoring techniques applied to continuous mixing process

Continuous manufacturing, and in particular continuous blending, can benefit from an on-line process monitoring technique at the outlet of the blender. As a result, sampling and sample analysis is eliminated, as well as sample preparation and sampling bias associated with the disruption and removal of material from the blender (McKenzie et al., 2006). Noninvasive techniques that do not disturb the powder during monitoring are very valuable since they analyze powder properties without affecting the operation of the blender and have an immense potential for being incorporated into a control system loop of continuous blending systems in a manufacturing setup (Pernenkil & Cooney, 2006).

The PEPT (positron emission particle tracking) technique offers the advantage of visualizing the dynamics while blending is in progress (Pernenkil & Cooney, 2006). In PEPT, the motion of a single positron-emitting particle is followed within the bulk flow in real-time. Spatial coordinates of the tracer particle are tracked as a function of time. It's possible to obtain quiver plots (displaying velocity vectors as arrows) of the axial and radial particles' trajectory during their travel along the blender (Laurent, Bridgwater, & Parker, 2000, 2002; Portillo et al., 2010).

Near-infrared spectrometry (NIRS) and light induced fluorescence (LIF) technologies have also been used as process analytical tools in a continuous mixer.

The NIRS method is based on the absorption of light in the wavelength region between 800 and 2500 nm (respectively 12821-4000 cm^{-1}) due to vibrations of molecular functional groups in the sample, mainly –CH, –OH and –NH bonds (Burns & Ciurczak, 2007). The no-need of sample preparation and the acquisition of several spectra in seconds by a noninvasive mode are some of the advantages that contributed to the wide application of NIRS as a PAT tool. In addition, both chemical and physical information from NIR spectra are obtained. There is a need for multivariate data analysis and chemometric methods to pretreat NIR spectra and extract relevant information, since they

are difficult to interpret. A linear relationship is often observed between the analyte concentration and the changes in spectra (Blanco et al., 2012).

Most of the studies using NIRS applied to continuous blending processes consisted of off-line monitoring of API concentration by retrieving samples at the outlet of the equipment followed by static spectra acquisition (Gao, Vanarase, et al., 2011; Portillo et al., 2008; Vanarase & Muzzio, 2011). Vanarase et al. (2010) described the first application of NIRS in on-line monitoring of a continuous mixing process. It focused on the development of a multivariate calibration model for real time predicting the API concentration in the out-flowing powder blend. A similar work was done by Martínez et al. (2013) and both reported NIRS as an effective PAT tool for real-time monitoring of a continuous blending process. In the recently developed continuous manufacturing PROMIS-line for tablets production (Simonaho et al., 2016) the monitoring of the blend homogeneity was done with in-line NIR.

Pernenkil (2008) used not only in-line NIRS but also LIF to study a continuous mixing process. The latter technique involves samples irradiation at a suitable wavelength for electrons excitation and evaluating the radiation emission at another wavelength (fluorescence). At low enough concentrations of the fluorescing molecule, the intensity of the emitted radiation is proportional to the concentration of that molecule in the blend (Lai et al., 2001).

No applications of Raman spectroscopy in continuous mixing were reported so far.

1.3. Pellets in pharmaceutical industry

In the pharmaceutical context, pellets can be defined as small, free-flowing, nearly spherical particles of a diameter between 0.5 and 1.5 mm, manufactured by the agglomeration of fine powders, typically drug substances and excipients (Mehta, Rekhi, & Parikh, 2005). Commonly, a hot melt extrusion (HME) process is used to manufacture them. In a typical HME process the solid materials melt and are mixed in the so-called plastification zone of the extruder. Next, the melt is forced into an extrusion die and solidifies at the outlet of the equipment. For the obtained strands to get a spherical shape, a hot-die face pelletizing unit or a spheronizer can be coupled to the outlet of the extruder (Treffer et al., 2014).

The usage of pellets in oral formulations is of greatest interest, since it is possible to increase poorly soluble drugs' bioavailability (Breitenbach, 2002) by forming solid

dispersions and solid solutions or to achieve sustained-release behavior (De Brabander, Vervaet, & Remon, 2003; Follonier, Doelker, & Cole, 1995). It also offers the possibility to administer incompatible drugs due to the multiparticulate system (Abdul, Chandewar, & Jaiswal, 2010). Pellets can be used as intermediates for capsule filling or tablet compaction and they have a spherical core that contains or is coated with the API, having one or more protective layers to control drug release (Jawahar & Anilbhai, 2012). The use of pellets also introduces some relevant advantages in the manufacturing process perspective. With highly uniform and spherical pellets, dosing precision increases as well as flowability; besides that, tableting of pellets results in reduction of dust (Treffer et al., 2014).

1.3.1. Segregation problems for pellets

It was mentioned that continuous manufacturing reduces powder segregation since the powder blends storage and handling is eliminated. However, usually this major problem remains when mixing formulations comprising pellets together with small particle sized excipients, due to their free-flowing property and natural tendency for size segregation.

Danckwerts (1952) proposed that there are two components of mixture segregation, namely the intensity and the scale. The intensity of segregation measures the spread of the concentration of the component of interest in the mixture. Alternatively, the scale of segregation reflects the state of subdivision into particle clumps. Evidently, the function of a blender is to reduce both the scale and intensity of segregation (Poux et al., 1991).

Small differences in either size, density or cohesive properties of materials in question are the most common causes for the segregating behavior (Ottino & Khakhar, 2000) and they are present in the kind of powders used in the present study. Besides this, Ottino & Khakhar consider some other scenarios: the circular or noncircular container's shape, the mixing equipment fill level and the materials similarity in shape.

1.3.2. Multiple-unit pellet system (MUPS)

Tablets containing pellets as a constituent are already a reality in the pharmaceutical industry. A tablet comprising a number of discrete particles such as pellets with one or more APIs being entrapped in or layered around cores is considered to be a multiple-unit

dosage form and more properly called multiple-unit pellet system (MUPS) (Reddy et al., 2011).

A new MUPS tablet production line has been developed by GEA to solve segregation problems and to eliminate production inefficiencies related with the damage of pellets' structure during compression (Vogeleer, 2014).

The aim of this dissertation is to contribute to the development of a continuous manufacturing line for tablets containing pellets by studying the mixing performance of the continuous blender for these formulations.

The dissertation is organized as follows. Materials, mixing equipment and feeder units used to study the continuous mixing process are described in Chapter 2. The work on the development of an analytical method to monitor the pellet concentration at the outlet of the continuous blender is presented in Chapter 3. The experimental conditions, setup, measurement and calculation of flow behavior and homogeneity indicators to study the continuous mixing process are described in Chapter 4. The presentation and discussion of results (Chapter 5) is divided into two parts. The first part focuses on the continuous blender characterization using RTDs and powder flow behavior indicators like hold-up, mean and bulk residence time, mean centered variance and number of blade passes as a function of different process parameters. The second part focuses on the effect of different process parameters on the blend homogeneity. Summary and conclusions are presented in Chapter 6.

Chapter 2 – Materials and Continuous Mixing Equipment

2.1. Mixture considered

The mixture under consideration in this study contains two components with different particle sizes: pellets and lactose monohydrate. The use of two ingredients with particle size distributions (PSD) that do not overlap is expected to facilitate the identification and quantification of each ingredient using on-line and off-line measurement tools that characterize the PSD of a sample. Therefore, one can easily identify the chemical composition based on size analysis.

The pellets used in all experiments are made from polyvinylpyrrolidone (PVP) polymer (Kollidon®, BASF, Germany) and were manufactured at RCPE by hot-melt extrusion (HME), followed by spheronization. Therefore, they present an approximately spherical shape as shown in Figure 3. These pellets don't contain any active pharmaceutical ingredient (API) in their composition and are characterized by this particle size distribution: d_{10}=793.66 µm; d_{50}=1318.04 µm; d_{90}=1662.61 µm. Pellets' true density is 1.1841 g/cm^3 and was measured using a helium pycnometer (AccuPyc® II 1340, Micromeritics).

Figure 3: Kollidon pellets.

The lactose monohydrate used was supplied by Meggle Pharma under the brand name Tablettose® 70 and is especially designed for direct-compression processes. It is manufactured by a continuous spray agglomeration process and the resulting lactose has a narrow particle size distribution: d_{10}=111.82 µm; d_{50}=207.45 µm; d_{90}=368.82 µm. The detailed particle size distribution information for each material can be found in Appendix 1 and 2 and it was measured using the Image Analysis Sensor QICPIC (Sympatec, Germany). Lactose's true density is 1.5422 g/cm^3 and was measured using the same helium pycnometer (AccuPyc® II 1340, Micromeritics).

The two materials comprising this binary mixture are considered to be non-cohesive and free-flowing powders. When pouring pellets onto a flat horizontal surface they rolled on it and spread over a large area, not accumulating in a pile (angle of repose is 0). Thus, these pellets have great flowing properties because of their nearly spherical shape and smooth surface. Lactose's technical flowability values reported by the supplier (MEGGLE, 2014) are in Table 2. It is possible to deduce its good/fair flowability feature, by comparing the angle of repose, Hausner ratio and Carr's index values with the defined ranges present in the Powder Flow chapter of the European Pharmacopoeia (2011).

Table 2: Flowability values of Lactose Tablettose 70® grade. Adapted from MEGGLE (2014).

Angle of repose (º)	Bulk density (g/L)	Tapped density (g/L)	Hausner ratio	Carr's index (%)
31	530	640	1.21	17.19

2.2. Continuous mixing equipment

The continuous blender apparatus used in this study is a Modulomix (manufactured by Hosokawa Micron B.V., The Netherlands) and is shown in Figure 4.

This blender falls into the category of convective mixers. A convective mixer design consists of a fixed internal rotating impeller containing paddles within a static

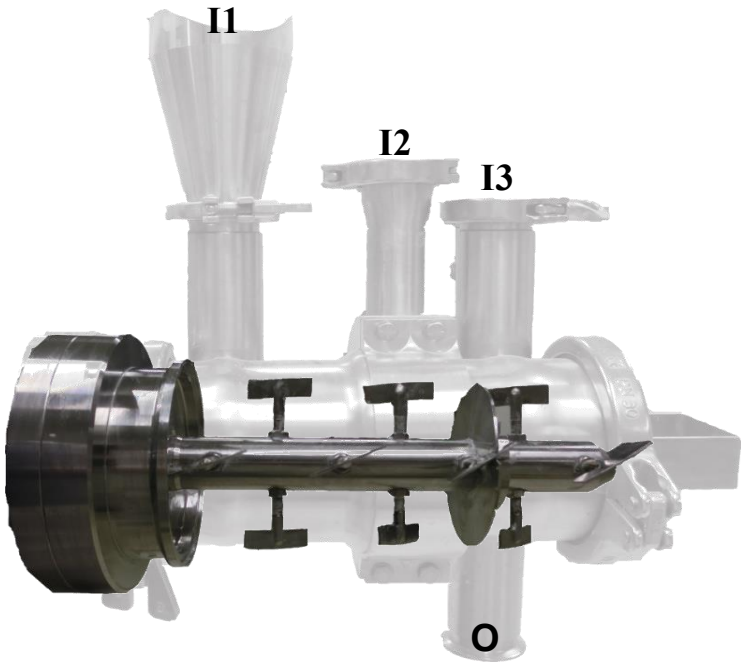


Figure 4: Details of the continuous mixer impeller design. I1, I2 and I3 are the blender's inlets and O is the outlet.

chamber (Harnby, Edwards, & Nienow, 1992). Due to the action of the impeller, particles are moved from one location to another within the bulk of the mixture.

The mixer has a 1.1 kW motor power and the rotation rates range from 100 rpm at a low speed to 1540 rpm at a high speed. The continuous dry powder mixer consists of a horizontal cylindrical process chamber in which a cylindrical and horizontal agitator with paddles is rotating (refer to Figure 4).

A detailed description of the mixer is as follows: The chamber is 30 cm long and its diameter is 13.5 cm. As the material enters the mixer, it crosses the pathway of 14 fixed blades, where 10 of them are flat rectangular blades (1.5 cm x 5 cm) and distance 3 cm from the impeller. The other 4 blades (2 immediately below the first inlet and the 2 in the other extremity of the blender) have a different shape, with the purpose of scrapping off the powder that could stick to the right and left walls. The paddles are fitted on the shaft in a fixed angle and are rotating at a fixed distance from the wall of the process chamber. The gap between the blender wall and the blades is less than 3 millimeters. The screw placed at the center of the frame is cylindrical with 30 cm long and 4 cm diameter. The angle of the blades with the horizontal shaft is 30 degrees.

The first inlet port (I1) was used for feeding both pellets and lactose and has a 5 cm diameter. The second (I2) and third inlet ports (I3, directly above the outlet O) were sealed during all experiments. The outlet of the mixer consists of a vertical open gate with a 5 cm diameter. The distance between the inlet I1 and the outlet is approximately 20 cm and corresponds to the total pathlength travelled by powders inside the chamber.

This mixer was developed to achieve powder mixing with short average residence times, as reported by the supplier (Hosokawa Micron, 2014).

In this study three different mixer speeds will be used: 100 rpm, 200 rpm and 300 rpm, which correspond to a Fr number of 0.7, 2.9 and 6.5, respectively.

2.3. Feeding systems

In the continuous mixing system used in this study, pellets and lactose were fed using two loss-in-weight (LIW) feeders, model K-SFS-24 manufactured by Coperion K-Tron (Figure 5a). Both materials were fed directly into the mixer inlet I1. The flow rate range of this model varies between 0.001 and 10 kg/h. The screw used was a twin concave design (Figure 5b).

LIW feeders constantly monitor the material's weight per unit time to achieve and maintain the predetermined feed rate. This kind of feeders consist of a hopper, weight-sensing device (load cell), feeding screw and controller. The actual rate of weight loss is compared to the set point and the feeder speed increases or decreases to compensate those fluctuations. Due to this control, LIW feeding is more accurate than volumetric feeding, in which the screw rotates at constant speed to discharge material at a predetermined volume-per-revolution rate from the hopper to the process (Nowak, 2010).

Thus, before each mixing run the desired feeding rate was set in the control panel.

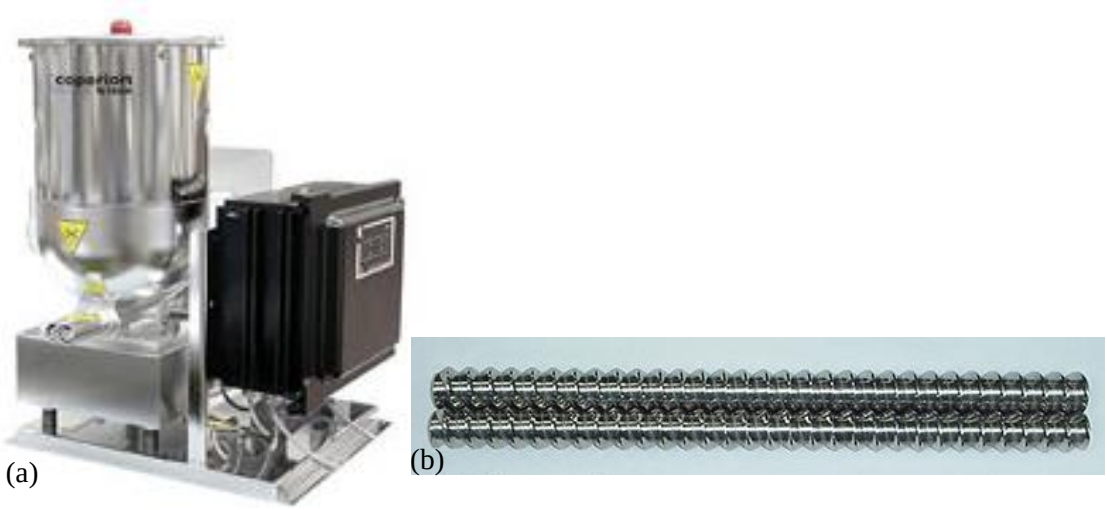


Figure 5: (a) Loss-in-weight feeder model K-SFS-24 by Coperion K-Tron. (b) Twin concave screw design, used to fed the materials in the present study. Retrieved from http://www.ktron.com/process-equipment/feeders/feeding-equipment/micro-compact-feeders.cfm

Chapter 3 – Development of an analytical method to monitor the pellet concentration at the outlet of the continuous blender

3.1. On-line method using near-infrared spectroscopy (NIRS)

Near-infrared spectroscopy was the first chosen PAT tool to build a calibration model to predict the pellet concentration at the outlet of the continuous blender and further on, to monitor the continuous mixing process. The focus on pellets as tracer material is because normally they carry the API in a final dosage form containing this multiparticulate system. In this current work, pellets are only placebo.

The choice of using NIRS is due to the well-known advantages of this technique, namely its noninvasive features, quick measurements and without the need of sample preparation. In addition, this technique has already been applied and reported as accurate to monitor the drug concentration and thus predicting the blend homogeneity in continuous mixing processes (Martínez et al., 2013; Vanarase et al., 2010).

The characteristics of the NIR spectrum require the use of softwares for multivariate data analysis to establish a quantitative relationship between the spectrum and the concentration of pellets in the analyzed sample. Therefore, the first stage in developing a NIRS procedure is building a calibration model. Here, a calibration method using partial least-squares (PLS) regression is applied.

PLS uses eigenvectors and eigenvalues to perform a decomposition of the spectral and correspondent concentration information simultaneously, to determine the most important variations in the data. In other words, PLS stablishes a linear combination between two matrices: the spectral data, in which the absorbance value for each wavelength represents one X variable; and the pellet concentration in each calibration sample, the Y variable. Thus, the dimensionality of the problem, initially with hundreds of X variables, is reduced to few factors, called latent variables. Each latent variable is a linear combination of spectral data. PLS eliminates variations in spectra that do not add useful information in establishing a calibration (Blanco et al., 2012; Lavine, 2000; Roggo et al., 2007).

3.1.1. Preparation of calibration samples

The calibration samples for the development of a quantitative model consisted in laboratory mixing and individual spectra acquisition. Eight calibration samples were

prepared in a tubular blender (Turbula® T2F Maschinenfabrik Willy A. Bachofen AG, Switzerland), each one mixed for 5 minutes at 32 rpm. In order for the calibration model to be useful when monitoring a continuous mixing process, mainly when dealing with RTD experiments within which the tracer (pellets) concentration in the binary mixture can vary from 0 to high values, the calibration samples were chosen to span a wide content range. Thus, the calibration samples consisted of 100 g of blends where pellets varied in concentration from 2, 5, 10, 20, 30, 40, 50 and 60% (w/w) diluted with lactose.

3.1.2. NIR Instrumentation, data collection and processing

NIR spectra were collected with the spectrometer SentroPAT FO (Sentronic GmbH, Germany), which is a diode array spectrometer. Spectra acquisition was done in diffuse reflectance mode over the wavelength range of 1100 – 2200 nm with a resolution value of 2 nm, which means that absorbance values were recorded at 2 nm intervals. Each spectrum is obtained through the average of 62 scans and the integration time is 0.016 seconds per spectrum, corresponding to the length of time when the detector in the spectrometer can capture light. As a result, approximately 1 spectrum was taken per second. The reference used has an absorbance value of zero and it reflects the light completely.

The software interface allows the bad spectra rejection. More specifically, spectra were taken with the *Outlier Check Enabled* parameter set ON, with a threshold value of 0.7. This means that spectra with absorbance values higher than 0.7 are not considered (it would correspond to low reflectance values, hence low NIR signal).

The probe consisted in a SentroProbe DR LS with a measurement spot of 5 mm diameter, approximately. The software SentroSuite 2.4 was used to control the spectrometer and to store the data from the calibration runs. NIR equipment is the same used by Wahl et al. (2013, 2014).

With the collected spectra, a chemometric model was built in SIMCA 13 (Umetrics, Sweden), where a pretreatment with Standard Normal Variate (SNV) followed by 2nd derivative was applied.

SNV is a scatter-corrective pre-processing method designed to reduce the physical variability between samples due to scatter and to minimize the spectral contribution of differences in particle size, which in fact occurs between pellets and lactose. It also adjusts the baseline shifts between samples. The transformation is applied to each spectrum

individually by subtracting the spectrum mean and scaling with the spectrum standard deviation (Barnes, Dhanoa, & Lister, 1989).

Two kinds of cautions were taken when applying the pre-processing. At first, scatter correction (SNV) should always be performed prior to differentiation (2^{nd} derivative) because the first one is designed for correction of raw spectrum and have never been thought of as a correction to a differentiated or baseline-corrected spectrum (Rinnan, Berg, & Engelsen, 2009). Since SNV does not involve a least squares fitting in their parameter estimation, they can be sensitive to noisy entries in the spectrum, so all the noise should be eliminated from the raw spectra before doing the SNV correction. In all the obtained spectra the noisy regions under 1150 nm and above 2120 nm were excluded before applying the pre-treatment.

On a first analysis, it may seem more appropriate to include in the model the information concerning the different particle size of the mixture. For this purpose, spectra should not be pretreated with SNV, which removes this physical effect. However, in all the performed experiences, as explained latter, there are differences in sample presentation, i.e., the quantity of powder passing in front of the NIR probe is not always the same. Thus, the light path length varies during the analysis of a given sample and due to that, there are scatter effects in the resulting spectra, which are removed by SNV.

Concerning the treatment with second derivative, it results in the removal of both baseline offset differences between spectra and differences in baseline slopes between spectra (Bakeev, 2005).

3.1.3. Experimental set-up for acquisition of NIR spectra

It should be ensured that the quantitative NIR model is produced with spectral data obtained under the same or very similar measurement conditions found in the process to be monitored (Blanco et al., 2012; Fonteyne et al., 2015). In this study, the monitoring at the outlet of the continuous blending equipment consists in measuring moving solids. Therefore, the calibration samples should be analyzed under the same moving conditions. However, it would be difficult to obtain calibration spectral data directly in the mixing process because it is very difficult to retrieve the same sample portion measured by the NIR probe at the outlet of the blender and send it to the laboratory to provide the reference data (corresponding pellets concentration). Alternatively, the process sample transporting system was simulated in the laboratory i.e. the two experiments carried out for acquiring

off-line NIR spectra from calibration samples consisted of replicating the possible ways to collect the on-line spectra at the blender outlet. Several spectra were acquired from each sample.

Figure 6: Experimental setup for off-line NIR spectra acquisition: (a) Funnel experiment, (b) Chute experiment, (c) Rotating plate experiment.

The first one consisted of making the calibration mixtures flow through a funnel (Figure 6a) which will be called *funnel experiment*. The NIR probe is focused onto the powder stream at the outlet of the funnel. An identical funnel would also be attached at the outlet of the blender to stream the powder in front of the NIR probe. The second setup for acquisition of NIR calibration spectra was slide the calibration mixes down on an inclined chute (Figure 6b), in order to reproduce, as faithfully as possible, the powder flow conditions in the outlet of the continuous blender, from now on mentioned as *chute experiment*. This type of chute could be placed at the outlet of the blender if the analytical method proves successful. The criteria to choose the chute inclination angle was visual analysis where powders exhibited a good slip behavior.

One of the challenges of measuring powders while they are moving is the different physical presentation of the sample to the probe, hence interfering with the acquisition of reliable results. That´s why the aforementioned measurements were taken with the parameter *Outlier Check Enabled* set as TRUE, which rejects spectra where the sample presentation is poor (i.e. there's no powder or only scarce is passing in front of the probe).

In all of the previously described situations, samples were poured by hand. Both in the chute experiment and funnel experiment efforts were made to drop each sample under a constant flow rate and at similar velocities between different samples. Since one spectrum was taken per second, if the sample takes 5 seconds flowing through the

funnel/chute, on the whole, 5 spectra were collected. If the powder flow was not continuous or if the powder slipped around the probe spot instead of passing in front of it, the outlier check parameter would reject that spectrum from the analysis.

As it will be later described in more detail, the calibration models for the methods described above do not lead to reliable models. Consequently, a third setup was built although it does not represent the real powder flow at the outlet of the continuous blending process. For that, the calibration mixes were placed on a rotating plate, which objective was provide a constant sample presentation to the spectrometer's probe and to allow the samples to move at a precise and controlled velocity. This approach for acquiring calibration spectra for monitoring a pharmaceutical process has been successfully applied before (Scheibelhofer et al., 2013) with the same NIR spectrometer (Wahl et al., 2014). The NIR probe is fixed above the rotating plate (Figure 6c). In the *Rotating plate 1* experiments the samples were mixed according to the conditions mentioned in 3.1.1. and in the *Rotating plate 2* experiment the samples were prepared like *Rotating plate 1* but spectra were collected in 3 different positions of the rotating plate, to avoid scanning of the same sample region after the first and second rotation.

3.1.4. Results and Discussion

The raw spectrum of pure lactose and pure pellets (without pre-treatment) are shown in Figure 7. These spectra were obtained as a log 1/R in the 1100 nm – 2200 nm range. Thus, the difference between both baselines is related to the unequal reflected light intensity by both materials. A baseline close to zero means that less light is being absorbed by particles and so more light is reflected and the NIR probe collects a more intense signal. As a result, by analyzing these two spectra it is possible to infer that the signal from pellets alone is very weak, while the incident light is extensively reflected by lactose.

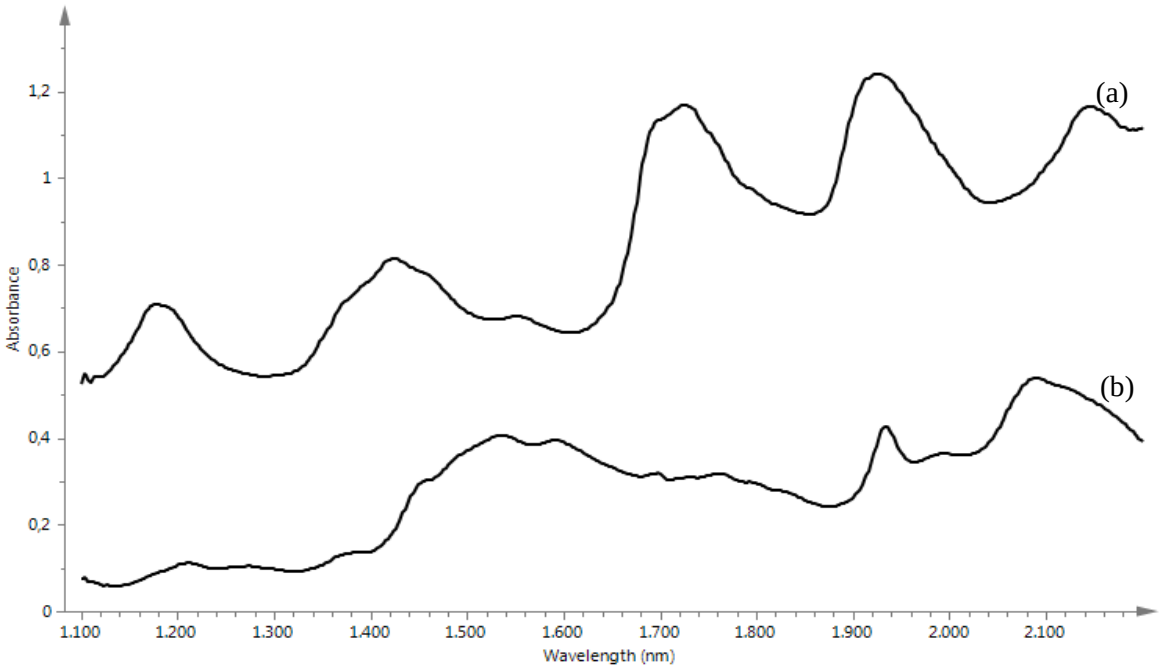


Figure 7: Pure pellets (a) and pure lactose (b) raw spectra, acquired in static mode.

The first PLS model was developed using calibration samples from the funnel experiment. Figure 8 presents all the collected spectra for this experiment after pretreatment with SNV and 2nd derivative.

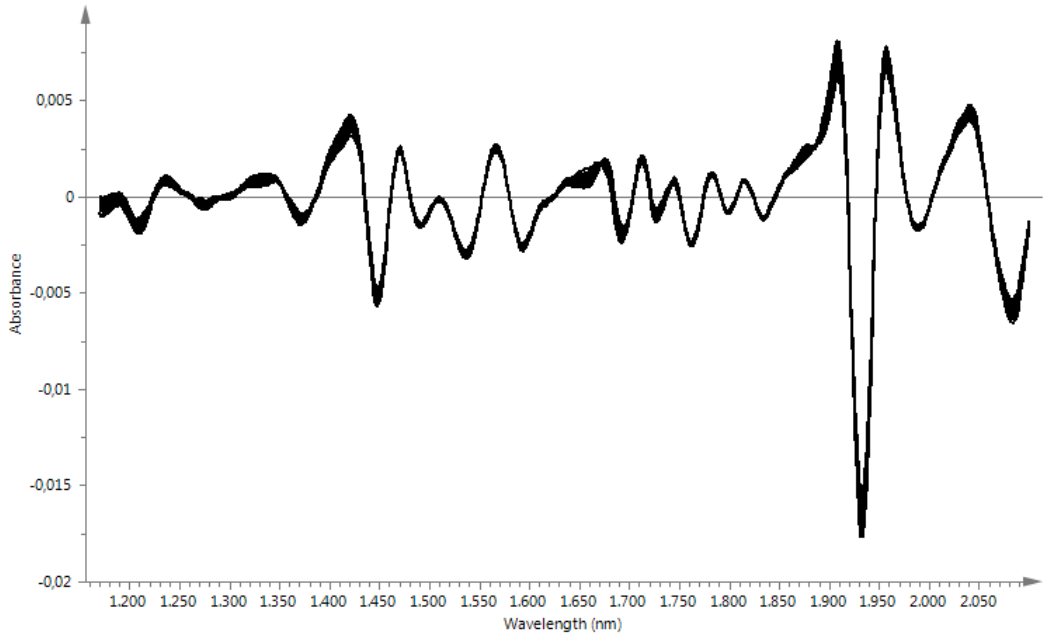


Figure 8: Calibration samples' spectra for funnel experiment, after pre-treatment with SNV followed by 2nd derivative. Plot obtained at SIMCA 13.

The spectral ranges chosen to develop this PLS model (and all the following presented models) were: 1170 – 1190 nm, 1320 – 1340 nm, 1400 – 1440 nm, 1640 – 1740 nm and 1860 – 1980 nm, within which the different pellet concentration groups are well-

separated and nearly equidistant. Since spectral differences due to light scattering were removed by pre-treatment, these spectral changes are due to content variations and should be included in the model.

Figure 9 shows the *observed vs predicted plot* given by SIMCA, constructed from calibration samples of the funnel experiment. It displays the relationship between the observed Y (pellet concentration known values) on the ordinate axis and the predicted Y (pellet concentration for each sample predicted by the obtained model) on the coordinate axis. In the X axis the pellet concentration values in each spectrum are displayed, as predicted by the PLS model.

The model obtained consists of 4 latent variables, which means that four most important linear combinations of spectral data explain a sufficient amount of the overall variation in pellet concentration between samples. Each latent variable contains information from each wavelength in the spectrum, some weighted more heavily than others.

In this kind of plot, two values are computed to evaluate the performance of the PLS regression model. The first one is root mean square error of estimation (RMSEE) and measures the fit of the model using the following equation:

$$RMSEE = \sqrt{\frac{\sum(Yobs-Ypred)^2}{N}} \quad \text{(Equation 3)}$$

where Yobs – Ypred refers to residuals, information not included in the mode. The lower the RMSEE, the better model obtained. The value obtained for this case is quite high, approximately 5.9.

The root mean square error from cross validation (RMSEcv) applies to the calibration workset (as does RMSEE) but indicates predictive power. It represents the model's error when doing cross validation, where one part of the calibration data is kept out of model development and predicted by it, thus acting like a validation set. The predictions of the kept out elements are compared to the actual values, so a small RMSEcv value is desired. This is not observed for the PLS model obtained with the funnel experiment samples, where the RMSEcv is 8.

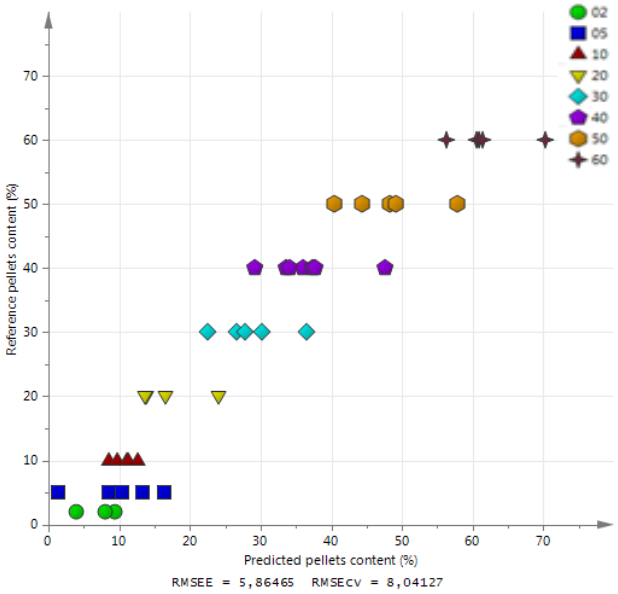


Figure 9: The chemometric model from 2% to 60% (w/w) pellets content in the calibration samples of the funnel experiment. The model obtained consists of 4 latent variables.

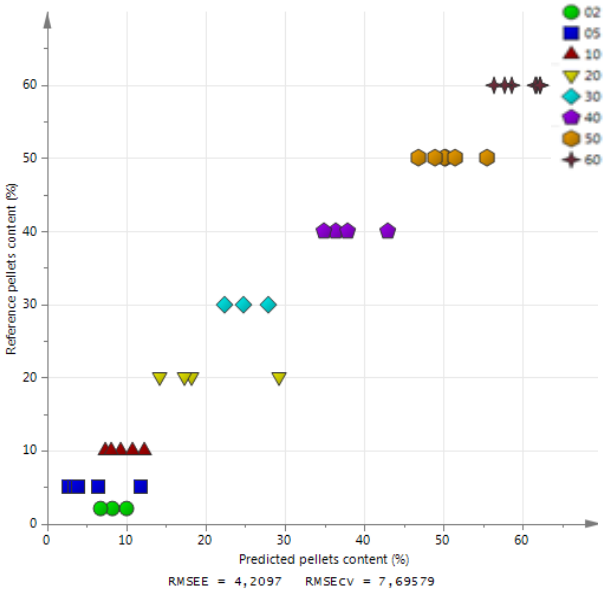


Figure 10: The chemometric model from 2% to 60% (w/w) pellets content in the calibration samples of the chute experiment. The model obtained consists of 5 latent variables.

Figure 10 shows the *observed vs predicted plot* for the obtained PLS model using the chute experiment samples as calibration set. Again, the RMSEE and RMSEcv remain high, with values of 4.2 and 7.6, respectively.

In addition, when watching the powder flowing down the chute, it seems that the pellets slid faster than lactose. In the first experiments done with the chute, it was observed that the chute's length was too large for the quantity of powder being analyzed. Most of the times, the sample slid around the NIR probe, instead of passing in front of it.

The *chute experiment* was repeated, this time narrowing the chute (using metallic adhesive tape) to avoid the powder to slip around the probe measuring spot, and forcing the powder to flow in front of it. To compare on an equal basis, the PLS model was built with the same conditions as the ones used in the first Chute Experiment (pretreatment using SNV followed by 2nd derivative, PLS model with 5 latent variables, Spectral ranges: 1170-1190nm, 1320-1340nm, 1400-1440nm, 1640-1740nm, 1860-1980nm). These experimental conditions did not improve the model's predictive features compared to the first one, as seen from the RMSEE and RMSEcv values, which are 5.1 and 11.5, respectively.

In the two performed rotating plate experiments, the previously mentioned parameter to exclude outlier spectra (*Outlier Check Enabled)* was turned OFF, because there is a continuous sample presentation to the NIR probe, and the powder is laid on the

rotating platform just below the probe. Figure 11 and 12 plot the theoretical and predicted pellets concentration in each calibration sample of the experiments rotating plate 1 and 2.

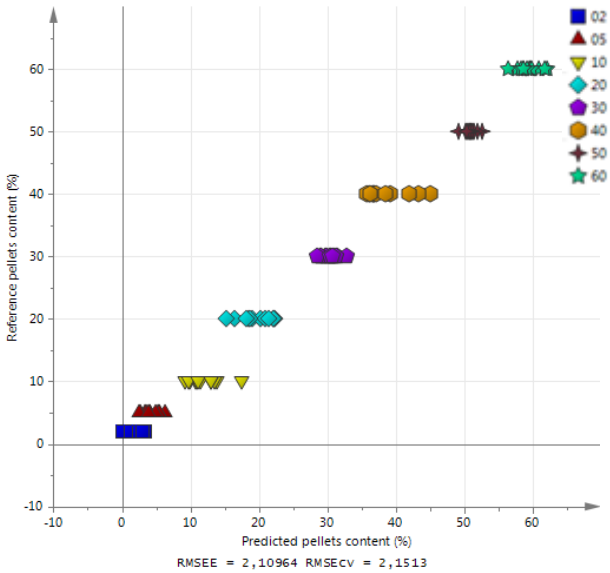


Figure 11: The chemometric model from 2% to 60% (w/w) pellets content in the calibration samples of the *rotating plate 1* experiment. The model obtained consists of 3 latent variables.

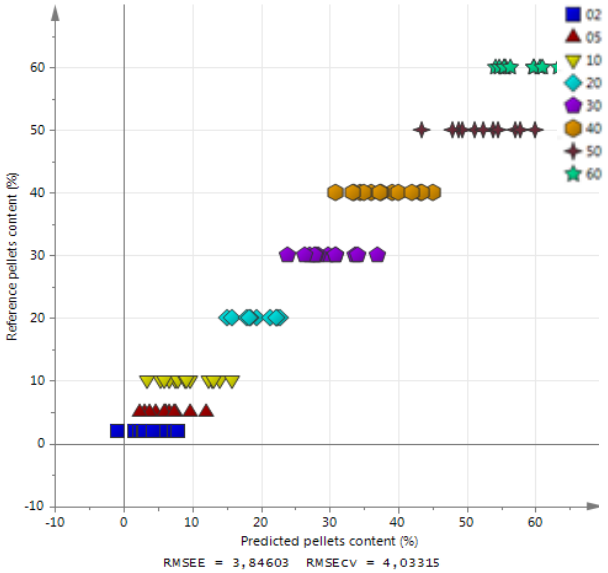


Figure 12: The chemometric model from 2% to 60% (w/w) pellets content in the calibration samples of the *rotating plate 2* experiment. The model obtained consists of 3 latent variables.

Since rotating plate experiments offered the most accurate PLS models, they were subsequently used to predict the pellets concentration of the data set from the other 3 experiments (funnel, chute and the other rotating plate). In this way, it's possible to verify if this setup for acquiring static calibration spectra is able to monitor the continuous blending process with flowing particles.

The predictive power of PLS models obtained with both rotating plate experiments is evaluated by the root mean square error of prediction (RMSEP). It corresponds to the standard deviation of the predicted residuals (errors) and is calculated the same way as RMSEE, with the difference that the predicted values correspond to a different dataset used for model's validation. This parameter is computed in the *Y PS plot* displayed by SIMCA (Figure 13 and 14) (similar to the observed vs predicted plot but using a prediction set different from the calibration one).

The models obtained with the rotating plate experiments have lower estimation errors (observable in plot's footer of Figure 11 and 12), but larger errors when predicting the dataset from chute/funnel (Table 3).

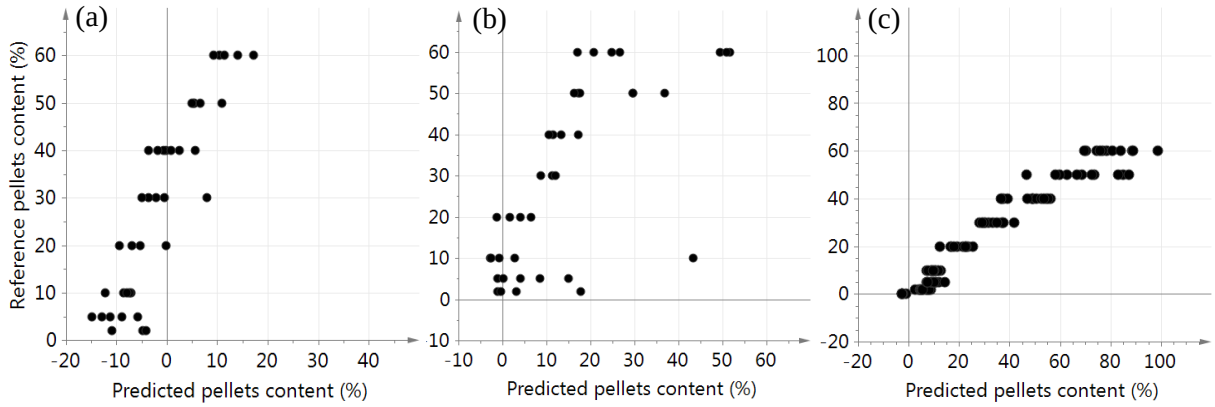


Figure 13: Prediction-set using the PLS model developed with rotating plate 1 calibration samples to predict the pellets content in samples from (a) funnel experiment, (b) chute experiment, (c) rotating plate 2 experiment.

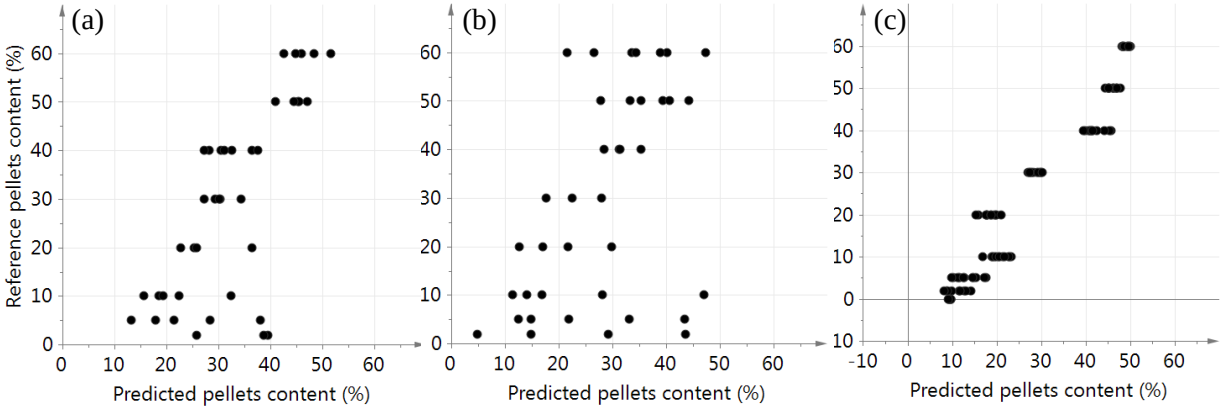


Figure 14: Prediction-set using the PLS model developed with rotating plate 2 calibration samples to predict the pellets content in samples from (a) funnel experiment, (b) chute experiment, (c) rotating plate 1 experiment.

Table 3: Root mean square error of prediction (RMSEP) when using the PLS model developed with rotating plate 1 and 2 calibration samples to predict the pellet content in the samples from the other experiments.

	Prediction-set			
	Funnel Exp.	**Chute Exp.**	**Rotating plate 1 Exp.**	**Rotating plate 2 Exp.**
PLS Model Obtained with Rotating plate 1 Exp.	29,1%	19,4%	-	11,5%
PLS Model Obtained with Rotating plate 2 Exp.	14,6%	19,2%	7,4%	-

Therefore, the results in Table 3 suggest that even the models acquired with the calibration samples rotating in a disk right below the probe can't be confidently used to predict the pellet concentration at the blender outlet, since the on-line monitoring of the mixing process would be done by placing a funnel of chute to concentrate the powder to the NIR probe.

An additional data treatment approach was carried out to test if the mix spectrum actually contains information about pellets and lactose. For that purpose, a MCR (Multivariate Curve Resolution) analysis was done in the MCR-ALS toolbox for MATLAB. The aim of MCR is the resolution of complex mixtures into pure-components contributions. In this case, the only constrain set in the program was that the two component mixture adds up to 100%. As a result, MCR indeed interprets the mixture 50% pellets + 50% lactose (from the experiment *rotating plate 2*) as being composed by pellets and lactose, but not in the correct proportion. The same way it happened with SIMCA outputs, MCR does not predict correctly the pellets concentration in different samples (see Appendix 3).

Finally, we test if the failure of all previous predictive methods is due to the large differences in absorbance for pellets and lactose (Figure 7). The *rotating plate experiment* was performed once again, this time using calibration samples containing calcium stearate pellets (the matrix carrier is unknown), which are visually less transparent (see Appendix 5) and have a higher signal in NIR (see Appendix 6). The aim was to test if pellet's transparency is responsible for the unsatisfactory obtained models. The models are not better (see Appendix 7 and 8) that for the Kollidon pellets.

3.1.5. Conclusions

The NIR predictive models obtained are not satisfactory for monitoring the continuous blending process. Remembering, the intention was to use the NIR model to predict the pellets concentration at the blender outlet, both to construct the residence time distribution curves of pellets and to assess the blend homogeneity. For that, the predictive model needs to accurately estimate the pellets content over a broad range of concentrations.

The first evidence that NIR was not correctly acquiring information about the content of samples is the visual appearance of the mixture of pellets and lactose (see Appendix 4). Pellets appear to be completely coated by lactose powder, which minimizes the signal from pellets even further.

Other possible explanations for not being possible to develop a good NIR method is the absence of a component/API inside the pellets (or in the coating) with characteristic absorbance peaks in near-infrared region.

It is known that the flow of bulk solids is a complex phenomenon in which powder moves at a certain velocity. The motion of particles produces changes in the density and distribution of the voids, thus influencing the NIR measurements and the predictive model's quality. It was observed that pellets flow faster than lactose particles and that there is some particle flow discontinuity. It was difficult to maintain a constant flow velocity, since the samples were poured manually in the chute and the funnel.

The efforts using chemical fingerprints are at this point abandoned and one proceeded with another particle property that differentiates the components in the mixture: PSD. Therefore, the continuous blender's residence time distributions are going to be assessed with pellets concentration calculated with off-line particle size analysis.

3.2. Off-line method using particle size analysis with Image Analysis Sensor QICPIC

Pellets and lactose have completely distinguished particle size profiles (Figure 15). This allows the concentration of pellets in a sample collected in the outlet of the continuous blender to be calculated using particle size analysis.

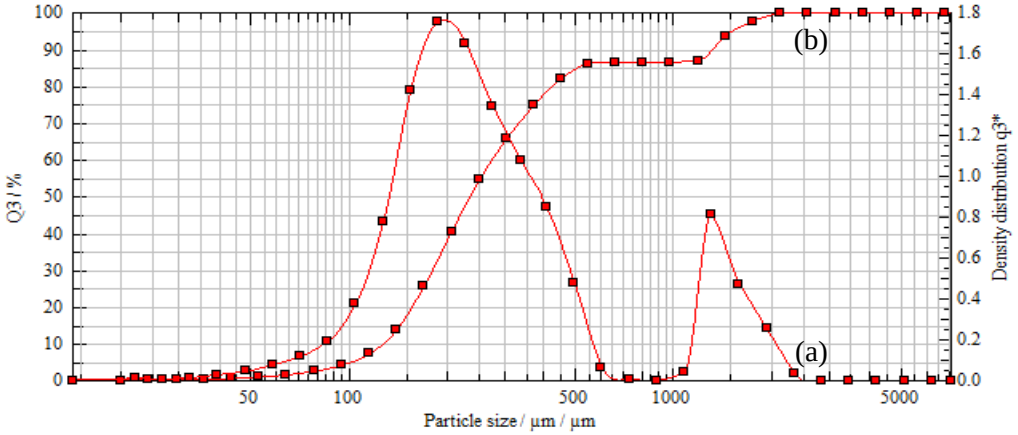


Figure 15: Particle size analysis of a mixture comprising lactose monohydrate and pellets at 10% (w/w). (a) Corresponds to the Gaussian distribution of particle sizes of lactose in the first and second peak, respectively. (b) Represents the cumulative distributions curve.

The equipment used in the particle size analysis is an Image Analysis Sensor QICPIC (Sympatec, Germany).

This equipment combines a dry dispersing unit with a vibratory feeder and a dynamic image analysis (DIA) system, which images a flow of moving particles (Köhler, List, & Witt, 2007; Witt, Köhler, & List, 2004) (Figure 16a).

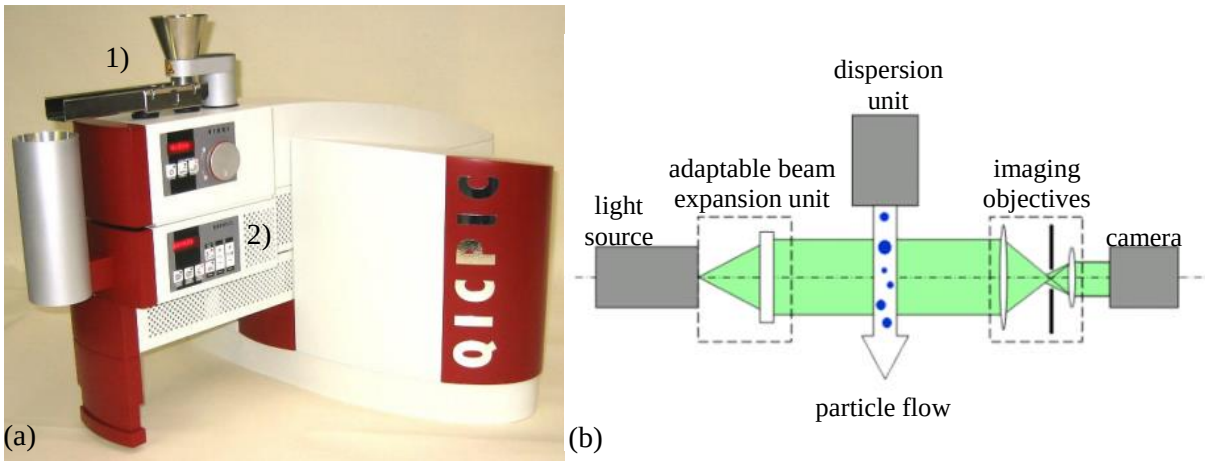


Figure 16: (a) Image Sensor Analysis QICPIC equipment set-up coupled with 1) dry vibratory feeder VIBRI and 2) dry dispersing unit RODOS. (b) Schematic presentation of the optical set-up of the QICPIC system. Both images were adapted from Witt *et al.*, 2004.

Compressed air is used to disperse the powders being analyzed and avoid particle overlapping in the detector. The particle flow is blown through the light beam and collected in a suction after the analysis (Figure 16b). While the dispersed particle flow is led through the image plane, they are lighted by a pulse light source and the particles' shape is acquired by a high speed CMOS camera. The recording starts when the camera detects the first particle.

For the assessment of particle size, the shadow of each particle passing in the front of the analysis window is turned into the diameter of a Circle of Equal Projection Area (EQPC). This corresponds to the diameter of a circle that has the same area as the projection area of the particle.

QICPIC is equipped with three imaging objectives for different magnifications. To analyze samples containing lactose and pellets, a low magnification was selected (in which 1 pixel corresponds to 20 µm) since one is dealing with coarse particles. The trigger condition parameter was set for 400 Hz, meaning that 400 pictures are taken per second. The dispersion system has a 10 mm injector, thus only particles with maximum size corresponding to half of the injector diameter are measured. The pressure of the injection air is 0.5 bar, a low pressure since one is working with non-cohesive powders.

In the software, we created a parameter called *%Pellets* which value gives the percentage of particles having sizes between 800 – 2000 µm, in the total analyzed sample volume. Note that the results of the QICPIC analysis are volume based and not mass based. Therefore, these values need to be corrected using the true density of the materials. To convert the obtained percentage of volume into pellets concentration in the analysed sample, it was necessary to measure the sample mass and take into account the true density of both pellets and lactose, applying the following equations:

$$V_{sample} = \frac{m_{sample}}{\%V_{pellets} \times \rho_{pellets} + \%V_{lactose} \times \rho_{lactose}} \quad \text{(Equation 4)}$$

$$c\ (\%w/w) = \frac{\%V_{pellets} \times \rho_{pellets} \times V_{sample}}{m_{sample}} \quad \text{(Equation 5)}$$

$$c\ (g/cm^3) = \frac{\%V_{pellets} \times \rho_{pellets} \times V_{sample}}{V_{sample}} \quad \text{(Equation 6)}$$

The figure below shows the QICPIC output for a sample with a known pellet concentration. In this case, the analysed sample had 50% (w/w) pellets and the resulting percentage of volume is 56.85%, corresponding to 50.29% (w/w) pellets concentration when corrected to the true density of the materials. With this example, it is demonstrated that this method's error is small.

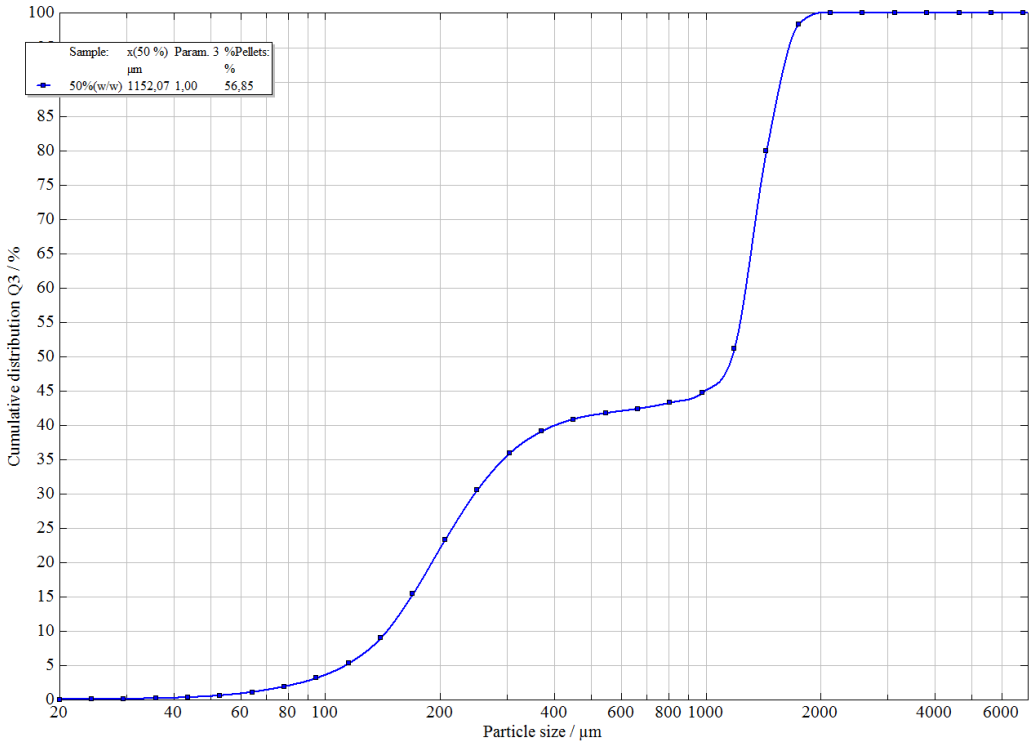


Figure 17: QICPIC's reported output for a known 10g sample containing 50% (w/w) pellets. Both particle size distribution of the mixture and percentage of pellets are plotted.

There are some disadvantages of using an off-line method to monitor the pellet concentration at the outlet of a continuous blender. Namely, 1) limited quantity of samples considered, 2) segregation can occur during sample collection and transport between continuous mixing set-up and the analytical laboratory (to avoid the latter, the entire sample is analyzed); 3) the large time required to perform the analysis; 4) destructive method – with this particular equipment it is not possible to recover samples.

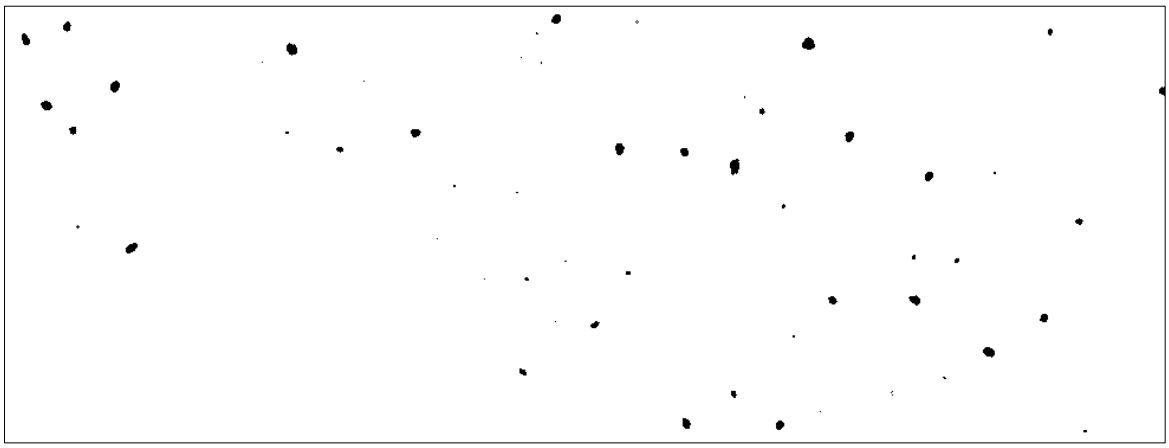


Figure 18: Appearance of the particle flow shadow projection during a sample analysis.

Chapter 4 – Methodology for continuous mixing study

4.1. Experimental conditions

The first group of continuous blending experiments were performed in order to characterize the powder flow behavior in the continuous mixer for different process parameters. More precisely, the combination of three different lactose flow-rates (2, 5, 8 kg/h) and three impeller rotation rates (100, 200 and 300 rpm) were studied. The various experimental conditions examined are presented on Table 4. Overall, nine experiments were performed.

The flow behavior in the continuous blender is assessed using residence time distributions which are measured by pulse injection method (Fogler, 2006; Vanarase & Muzzio, 2011). It consisted in feeding gravimetrically the bulk material (lactose) until steady state flow is reached inside the blender. Initially, the blender was ran during 5 minutes, only with lactose, to leave sufficient time for the bulk flow to reach the steady state. Then, a certain quantity of tracer material (pellets) was inserted manually in the inflow stream as an instantaneous pulse at time t = 0. The quantity of pellets injected in each experiment is stated in Table 4.

Table 4: Conditions used in the pulse injection experiments.

Exp. No.	Lactose flow-rate (kg/h)	Pellets injection (g)	Rotation rate (rpm)	Sampling periodicity	No. of Samples
1	2	30	100	10 s	31
2			200		
3			300		
4	5	100	100	5 s	36
5			200		
6			300		
7	8	120	100	5 s	39
8			200		
9			300		

The monitoring of a continuous blending process is performed at the outlet of the blender. Since it was not possible to use an on-line monitoring method, samples were manually collected in the outlet of the blender at various times (starting in time t = 0).

The sampling strategy will be described in the following section. The sample collecting stopped when there was no pellets coming out in the mixture, by visual inspection. The collected samples were analyzed on the QICPIC equipment for particle size analysis to measure the pellets concentration, as explained in Section 3.2. The target sample mass was between 5g and 10g of powder. This allowed the sampling to take place every 10 seconds on 2 kg/h experiments and each 5 seconds on 5 and 8 kg/h flow rates.

A second experimental investigation was carried out to study the mixing performance of the blender for the same materials. The continuous mixing experiments performed to assess the blend homogeneity are resumed in Table 5.

Table 5: Conditions used in the step injection experiments.

Lactose flow-rate (kg/h)	Pellets flow-rate (kg/h)	Pellets fraction (%w/w)	Rotation rate (rpm)
2	0,86	30%	100
			300
	0,11	5%	100
			300
5	2,14	30%	100
			300
	0,26	5%	100
			300
8	3,43	30%	100
			300
	0,42	5%	100
			300

Once again, the process parameters studied were flow rate (2, 5 and 8 kg/h for the bulk material lactose) and a high and low impeller rotation rates (100 rpm and 300 rpm). Another objective was to study the effect of two different formulations, i.e. the mass fraction of pellets flowing inside the blender was set as 30% and 5%. The corresponding pellets flow-rates used to achieve this proportion is shown on Table 5.

The 30% of pellets fraction is to simulate a typical formulation of tablets containing pellets. Although some published results report that is possible to obtain tablets with homogeneous pellet-distribution and good crushing features using 70% w/w of pellets (Wagner et al., 2000; Wagner, Krumme, & Schmidt, 1999), non-reported results obtained at RCPE suggest that more than 30% of this particular kind of pellets don't lead to tablets with enough strength. Tablets were produced under different compaction pressures with the same pellets used in this study. The results show that tablets containing above 10%

w/w pellets in a microcrystalline cellulose matrix do not have enough mechanical strength. The same is observed for tablets with over 30% w/w pellets in a lactose monohydrate tablet matrix. Above this pellets' mass values, tablets broke into pieces easily after compression.

A mass fraction of 5% of pellets inside the blender is to simulate a low dosage drug product carried by pellets in the final tablet (for example a high potency drug) and to test if pellets segregate more easily when used in a low proportion.

The step injection method was used, in which tracer material is added into the blend at time t = 0 at a constant feeding rate (Fogler, 2006). The system needs to be under constant bulk flow (steady state) and for that the blender was ran only with lactose being fed for about 5 minutes. These experiments consisted in running the blender during 10 minutes with both pellets and lactose being fed by a gravimetric feeder. To determine the homogeneity of the stream coming out of the blender, samples were collected at the outlet. During the first two minutes of run, samples were taken every 10 seconds and then every 20 seconds until the end of the experiment, adding up to a total of 36 samples for each experiment. Again, the pellets concentration in each sample was measured using QICPIC equipment. All data was processed in Microsoft Excel 2013.

The experimental setup is shown in Figure 19. The Hosokawa continuous mixer is integrated with K-Tron feeders. Note that in the pulse injection experiments, there was only one feeder working and in step injection runs both feeders were assembled, the right one feeding pellets and the left one feeding lactose.

Figure 19: Experimental setup for continuous blending study.

4.2. Sampling strategy

Since the on-line method to monitor the blending process were not satisfactory, an off-line method was applied and samples were manually collected. The sampling procedure consisted in placing a small plastic vial with 100 mL capacity under the blender outlet, at regular time intervals, collecting samples with mass between 5g and 10g, approximately. This was the target range, note that samples had mass slightly under or above these values, since the container fill level was visually monitored.

According to FDA's guidance which assesses adequate powder blend sampling, it must be done at the scale of scrutiny (scale of examination). This corresponds to the scale of the unit dose that a patient may take (FDA, 2003). Thus, the sample size should range between 10 mg and 5 g. In the present case, it was neither feasible to collect samples with the same mass nor having a sample mass fluctuating in the mentioned span. The second one is due to the fact that to have a representative result at QICPIC, the quantity of material being analyzed needs to be higher than 5 g, preferably.

4.3. Measurement and calculation of flow behavior and homogeneity parameters

Residence time distribution (RTD)

The RTD is determined using pulse input experiments, which experimental procedure was described in Section 4.1. The RTD curve is obtained by the following equation and by knowing the pellets concentration c over time (P. V. Danckwerts, 1953):

$$E(t) = \frac{c(t)}{\int_0^\infty c(t)dt} \quad \text{(Equation 7)}$$

E(t) is called the residence time distribution function and describes in a quantitative manner how much time different particles have spent in the mixer.

After plotting pellets concentration c as a function of time, the E(t) curve is obtained from the c(t) curve just by dividing c(t) by the integral $\int_0^\infty c(t)dt$, which is just the area under the c curve (AUC). The AUC was calculated using the trapezoidal method.

It is very common to compare RTDs by using their moments instead of comparing their entire distributions. For this purpose, two moments will be considered. The first moment is the mean residence time and the second one is called mean centered variance.

Mean residence time (MRT)

The mean residence time indicates the average time that a portion of the powder spent inside the continuous blender (Cullen et al., 2015) and is calculated from the RTD measurements applying the following equation:

$$\tau = \int_0^\infty t\, E(t) dt \quad \text{(Equation 8)}$$

A high mean residence time indicates that the tracer material spends a larger time inside the blender, allowing the materials to have more time to blend within the bulk material.

Mean centered variance (MCV)

A widely used measure of dispersion is the dimensionless variance of the RTD. The mean centered variance (MCV) is an efficiency indicator of a continuous mixer at specific operating conditions (Cullen et al., 2015) and will be calculated using the following equation:

$$\sigma_\tau^2 = \frac{\int_0^\infty (t-\tau)^2 E(t) dt}{\tau^2} \quad \text{(Equation 9)}$$

The MCV value usually varies between 0 and 1. For a perfectly mixed system, which is often described as a continuous stirred tank reactor (CSTR), the MCV is equal to one. For a perfect unmixed system, normally referred as a piston flow reactor (PFR), the MCV is equal to zero. A real blender will have something less than complete mixing but more than the limiting case of complete segregation. Thus, a higher value of MCV indicates better axial mixing efficiency of the blender. Since the RTD arises from the particles velocity in the axial direction (P. V. Danckwerts, 1953), the calculated MCV refers to the mixing in axial direction.

Mass hold-up

The hold-up mass is the amount of material present inside the continuous mixer at a given time (Cullen et al., 2015). Hold-up can be assessed by simultaneously monitoring the weight of material exiting the blender and the amount of powder being fed into the mixer, from process start-up until it reaches the steady state (Vanarase & Muzzio, 2011). Another way to measure non-invasively the hold-up mass would be to mount the continuous mixer on a load cell. When the flow is initiated, the powder hold-up increases until it reaches a plateau; when the mixer is operating under constant hold-up it is

considered to be in steady state (i.e., the amount of material being fed and exiting the blender is equal). The mass hold-up was measured by emptying the blender by hand at the end of each experiment and weighing this material sample. For that, the blender and the feeder were turned-off at the same time.

Number of blade passes/Shear intensity

Based in the powder hold-up, it is possible to determine the amount of mechanical energy experienced by the blend as it flows through the mixer.

The average number of blade passes was used to measure the shear intensity the powder experiences, and its effects on blending performance and is measured using the following equation:

$$N_p = \omega \times \tau \quad \text{(Equation 10)}$$

where ω is the impeller's rotation rate and τ is the mean residence time. In a continuous mixer, energy input is provided by impeller rotation. Since the impeller rotation rate has an effect on the mean residence time, the strain, which is proportional to the product of the shear rate and the mean residence time, can be calculated in terms of the number of blade passes.

Bulk residence time

The hold-up measurements can be used to calculate the bulk residence time of the lactose powder in the mixer (Vanarase & Muzzio, 2011):

$$Bulk\ residence\ time = \frac{hold\ up}{bulk\ flow\ rate} \quad \text{(Equation 11)}$$

Relative standard deviation (RSD)

In the pharmaceutical industry, the acceptance of a good blend is usually based on the common mixing index relative standard deviation (RSD) of the concentration of the component of interest in the blend, usually the active pharmaceutical ingredient (FDA, 2003; Pernenkil & Cooney, 2006).

The homogeneity of samples retrieved from the output of the blender is measured by calculating the variability in pellets concentration. The RSD is the coefficient of variability that will be used in this study to assess the blend homogeneity. It represents the sample standard deviation expressed as a percentage of the mean:

$$RSD = \frac{s}{\bar{c}} = \frac{\sqrt{\frac{\sum_1^N (c_i - \bar{c})^2}{n-1}}}{\bar{c}} \quad \text{(Equation 12)}$$

where c_i is the sample pellets concentration collected at time t_i, $\bar{c}$ is the average concentration over all samples, and n is the number of samples being considered.

Chapter 5 – Results and discussion of blender characterization

5.1. Residence time distributions

In this section, the continuous blender is going to be characterized using RTD. More specifically, the effect of different lactose flow rates and different impeller rotation rates on RTD and flow behavior parameters will be analyzed. For this purpose, nine continuous mixing runs were performed, which experimental conditions and procedures are described in detail in Sections 4.1 and 4.2.

First, there are some observations about the realized powder behavior in the course of the performed experiments that need to be mentioned.

For low feeding rates (2 kg/h experiments), materials leave the blender in periodic pulses rather than steadily. That means that the performance of the blender is not steady at 2 kg/h, which is the lowest throughput value suggested by the equipment manufacturer (Hosokawa). These fluctuations would be detected by on-line PAT, however they are not observable with an off-line method. Moreover, these fluctuations are averaged over the timespan of the sample collection. For higher throughputs, the mixture leaves the blender in a steady flow.

In all pulse injection experiments, immediately after pellets' injecting, the steady state of the bulk flow was disturbed and it was observed that the outcoming stream becomes larger. The lump of pellets affects the flow inside the blender due to its bigger size than the bulk lactose particles. Pellets are then "washed out" by the stream of bulk lactose that is constantly running through the blender. A larger lactose flow is expected to wash out the pellets more quickly.

In all experiments dust generation was observed, more extensively when using high rotation rates.

Residence time distributions under different flow rates and rotation rates are compared in Figure 20.

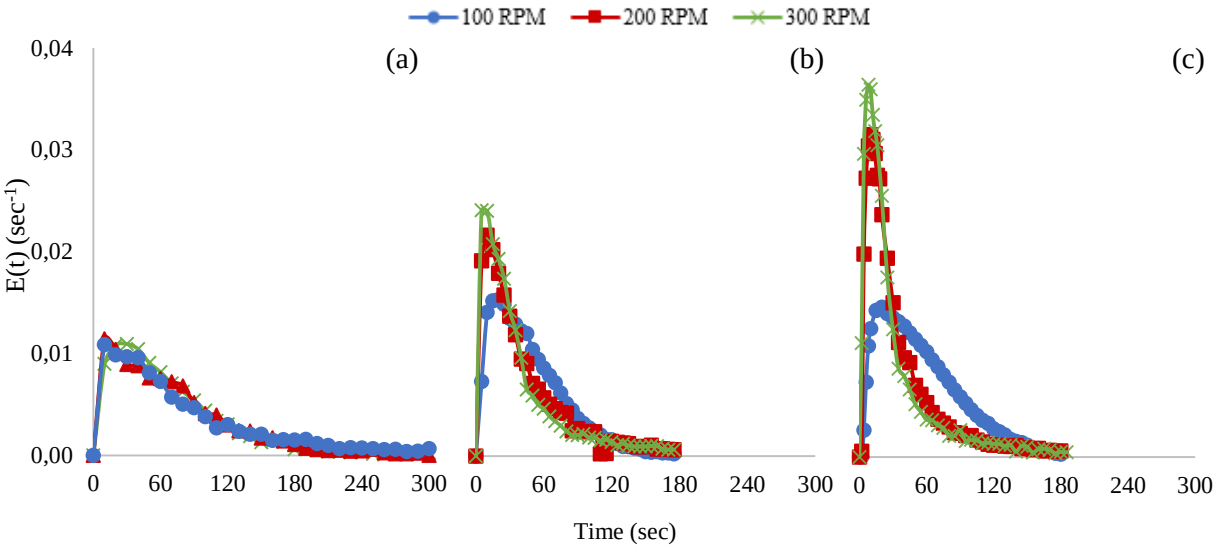


Figure 20: Residence time distribution curves from pellets particles as a function of rotation rate and lactose flow-rate: (a) 2 kg/h, (b) 5 kg/h, (c) 8 kg/h.

In residence time distribution curves, there are two attributes to be analyzed: the width and the slope of the distribution. Typically, the width of the RTD is used to determine the average time the powder stays within the system. The slope captures the dynamic rate at which the pellets (or a tracer) leaves the mixing chamber.

As illustrated in Figure 20, rotation rate only affects the width of the residence time curve when feeding lactose at 5 kg/h and at 8kg/h and from 100 rpm to 200 rpm. For 2 kg/h flow rate, RTD curves overlap with each other and there is no clear effect of blender rotation rate. This effect of impeller rotation speed on RTD width is less significant when increasing from 200 rpm to 300 rpm. The only observable differences between 200 rpm to 300 rpm is the magnitude of the peak of the RTD curves. Lower blade speeds lead to wider RTD. This is reasonable because a slower moving blade allows the pellets longer residence time inside the blender and the chance to mix. A high rotation speed pushes the pellets lump through the blender faster and giving less chance to mix with the matrix.

The effect of feeding rates on RTD can also be observed in Figure 20. The curve slopes are steeper for 5kg/h and 8 kg/h feeding rates than for 2 kg/h feeding rates at 200 rpm and 300 rpm rotation rates. The pellets are carried out and washed out of the blender more quickly by the larger flow rates.

Higher impeller rotation rates combined with high feeding rates lead to narrower RTD. However, it seems that RTD width is more sensitive to feed rate than to impeller rotation rate.

The AUC of a RTD curve should be read as the fraction of material exiting the blender that has spent time between t and t + dt inside the blender. As an example, in the experimental run with 2 kg/h lactose feed rate and 100 rpm rotation rate, 54.3% of the injected pellets spent one minute or less inside the blender. In Table 6 is stated the percentage of the injected pellets that spent 1 minute or less inside the blender.

Table 6: Fraction of the total injected pellets spending 1 minute or less inside the continuous blender, in each experimental conditions performed in the pulse injection experiments.

Exp. No.	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**
% pellets	54.3	50.9	51.7	70.6	77.4	80.4	61.2	82.0	83.9

The figure below shows the effect of both flow-rate and impeller rotation rate on powder hold-up inside the blender, pellets' mean residence time, mean centered variance and the strain experienced by the powder. The equations to calculate each of these parameters is described in Section 4.3.

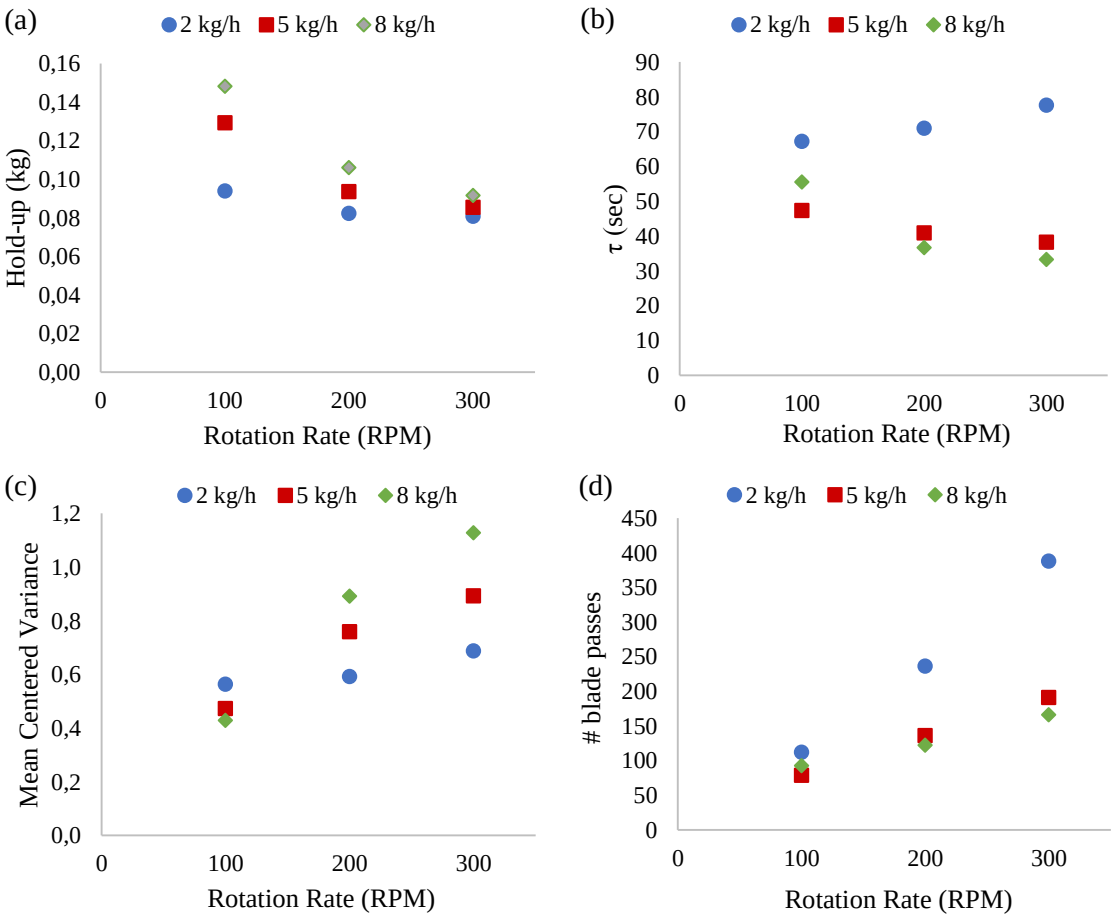


Figure 21: Effect of process parameters rotation rate and flow-rate on (a) hold-up, (b) mean residence time, (c) mean centered variance and (d) number of blade passes.

Table 7: Powder flow behavior parameters calculated for each experiment.

Flow-rate (kg/h)	Rotation rate (rpm)	Hold-up (kg)	Mean residence time (sec)	Mean centered variance	Number of blade passes	Bulk residence time (sec)
2	**100**	0,094	67	0,56	112	169
	200	0,082	71	0,59	237	148
	300	0,081	78	0,69	388	146
5	**100**	0,129	47	0,47	79	93
	200	0,094	41	0,76	136	67
	300	0,085	38	0,89	191	61
8	**100**	0,148	56	0,43	93	67
	200	0,106	37	0,89	122	48
	300	0,092	33	1,13	166	41

The effect of flow rate and rotation rate on each parameter (each column in Table 7) will be described sequentially, starting with hold-up mass in the blender.

A high hold-up indicates that the average time that the powder as a bulk spends in the blender is longer, having more time to mix. It also indicates that the powder will experience more shear provided by the blade as it travels through the mixer. As shown in Figure 21a, the hold-up mass decreases when increasing the rotation rate and it increases when increasing the bulk feeding rate. The maximum retained mass (in steady-state) is equal to 148 g and corresponds to the highest flow rate and lower rotation speed, while the smallest hold-up is reached for the lowest low rate and the higher blade speed that were investigated. High input of material (allowing higher blender fill level) combined with lower rotational speeds (not pushing material to the outlet) leads to material accumulation inside the equipment. The same results were obtained by (Vanarase & Muzzio, 2011).

Just like other authors reported, as the rotation rate and flow rate increase, the mean residence time of tracer material decreases (Portillo et al., 2008; Vanarase & Muzzio, 2011). We indeed observe the same for the 5 and 8 kg/h experiments. However, there seems to be some back-mixing or retention when using low throughputs and high rotation rates (2 kg/h, 300 rpm), because the mean residence time of pellets is high, contrary to expected.

At high rotation speeds, the powder experiences greater shear forces in the radial direction. As mentioned before on Section 2.2, the Froude Number that characterizes the mixer at 300 rpm is high, meaning that centrifugal forces are predominant. Thus, it seems that the incoming stream does not have sufficient volume to “capture” and push pellets to

the end of the blender, then they spend more time having radial mixing instead of moving in the axial directing thus having higher mean residence time. Maybe the 2 kg/h feeding rate is a too low stream for this kind of material and the number of spiral loops that pellets make within the vessel are higher before being carried away by the flow of lactose. The existence of back mixing can be questioned and could equally explain the high mean residence time of pellets in the referred operational conditions.

The effect of flow rate and rotation rate on the mean centered variance (MCV) will be discussed now. Since MCV arises from RTD and, in turn, RTD is related with particles velocity in the axial direction, a higher MCV value indicates better axial mixing efficiency of the blender. At 100 rpm, MCV values are similar regardless of the flow rate used. These suggests that in these conditions a similar degree of axial mixing is obtained. For the other two rotation rates studied (200 and 300 rpm) MCV increased when increasing the feeding rate. For the same flow rate applied, MCV increased when impeller rotation velocity increased. Thus, increasing rotation rate gives rise to better axial mixing. However, faster rotation rate also decreases the time available for mixing (lower residence time). These are opposing effects in achieving a good mixing.

Impeller rotation rate and the bulk feeding rate affect the number of blade passes through the powder bed (or hold-up mass). A larger number of blade passes typically correlates with a more homogeneous blend but could also indicate excessive exposure of pellets to shear and be an indicator for pellet attrition. As mentioned in Section 4.3, the average number of blade passes the powder flow experiences during its residence time in the mixer is dependent on the impeller velocity. For the same impeller rotation rate, there are no significant differences between the shear that the powder experiences when the bulk was fed at 5kg/h and 8 kg/h. This is due to the similar mean residence time values obtained in these experimental conditions. Although at higher rpm the powder remains within the mixer for a shorter time, the actual number of blade passes is larger than at the lower impeller velocity as shown in Figure 21d. In the experiments in which the lactose was fed at 2 kg/h, the shear that the powder experiences increases significantly, when the rotation rate or the feeding rate are increased. This is due to the high residence time observed in these experimental conditions and which unexpected behavior was explained before. As the powder spends more time inside the blender, it suffers more shear intensity when increasing the rotation rate.

Finally, we study the effect of flow rate and impeller rotation rate on bulk residence time. Since the hold-up is the quantity of bulk material inside the mixer when it's

operating under steady-state condition, the mean time that lactose particles spend inside (bulk residence time) is calculated as the ratio between the hold-up mass and the lactose feeding rate for each performed experiment.

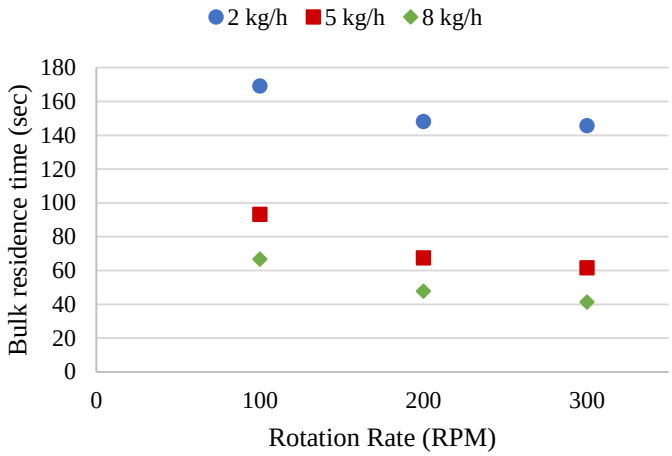


Figure 22: Effect of process parameters rotation rate and flow-rate on the residence time of the bulk lactose.

Lactose (bulk) residence time is highly affected by its flow rate and not greatly influenced by impeller rotation rate, for the same feeding rate. Comparing these values with the mean residence time of pellets (Table 7), it is clear that pellets flow faster than lactose.

For segregating blends such as the one used in this study, it should be investigated both RTD for pellets and the bulk material lactose, since they seem to have different residence time inside the blender. The RTD for the bulk material can be investigated using tracer experiments. This tracer must have a particle size similar to lactose or be a smaller and cohesive powder in such a way that its particles adhere to lactose and coat it, thus having the same flow behavior and residence time as lactose.

5.2. Characterization of the blend homogeneity

This section focus on the characterization of blend homogeneity as a function of process parameters: two different mixer rotation rates (100 rpm and 300 rpm) and three different flow rates for the bulk material (2, 5 and 8 kg/h). Additionally, two different formulations/pellets proportion inside the mixer bulk were considered. The first one, approximately 30%, which corresponded to pellets feeding rates of 0.86, 2.14 and 3.43 kg/h. On the other hand, it was studied the possibility of efficiently mix 5% of pellets

within the bulk lactose, simulating a situation where a low dosage drug product would be carried by pellets in the final tablet. Thus, pellets were fed at 0.11, 0.26 and 0.42 kg/h. A total of 12 experiments were performed. The number of samples taken in each experiments is 36, except for the experiment 1 and 2, because the blender suddenly stopped at the 8th minute, due to electrical problems.

Figure 23 are plots the measured pellets concentration for a 10 minute continuous blending process, in which pellets were fed to yield a formulation of 30% w/w of pellets.

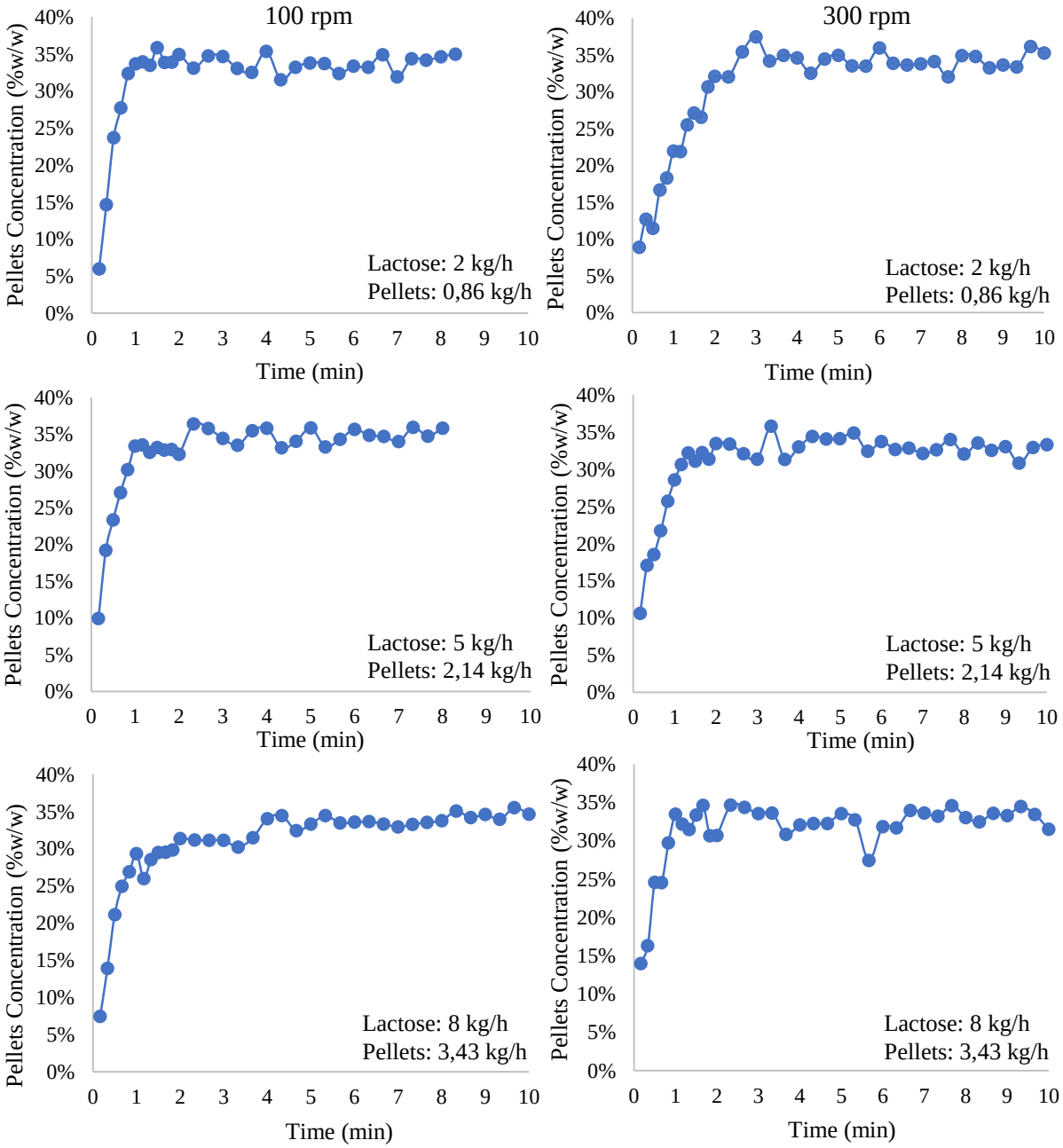


Figure 23: Measured pellets concentration for a 10 minutes continuous blending process. From left to right, the rotation rate increases from 100 rpm to 300 rpm. From up to down the bulk flow rate increases from 2 kg/h to 5 kg/h and 8 kg/h. All these experiments were performed with 30% (w/w) of pellets inside the continuous blender.

Given the results discussed before, a continuous blending run of 10 minutes corresponds to approximately ten (and in some cases more) times the mean residence time of pellets.

Continuous processes need to reach steady state quickly to avoid wastage of product. In the continuous mixing runs represented in Figure 23, the steady state seems to be reached between the first and third minute in the first four plots. Increasing the impeller rotation rate (left side plots vs right side plots) the blender takes more time to reach the steady state. No particular effect on reaching steady-state is observed as a function of the feeding rate of lactose and pellets. In general, it is not easy to deduce when the system got in steady state (and in particular when the feeding rate was set for 8 kg/h,). For that reason, the relative standard deviation (RSD) of these experiments was calculated using the last collected samples, more precisely from samples collected from 3min40sec on until the end, for compare on an equal basis.

In Figure 24 are plotted the measured pellets concentration for a 10 minutes continuous blending process, in which pellets were fed to yield a formulation with 5% w/w of pellets.

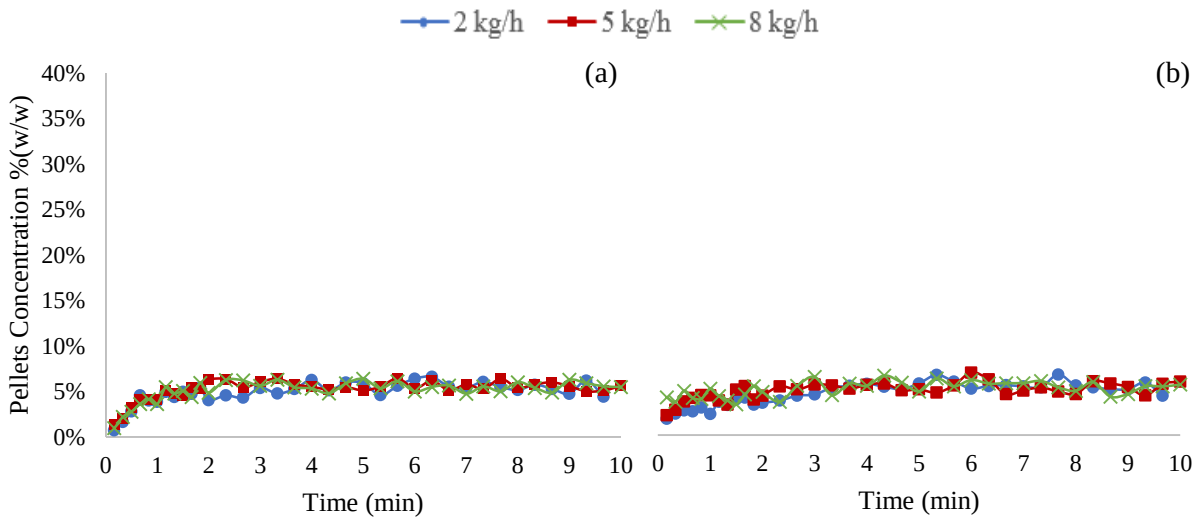


Figure 24: Measured pellets concentration for a 10 minutes continuous blending process. (a) Impeller rotation rate: 100 rpm, (b) Impeller rotation rate 300 rpm. All these experiments were performed with 5% (w/w) of pellets inside the continuous blender.

Comparing visually these two plots with the ones illustrated in Figure 23, it is noticed that the amplitude of variation in pellet concentration in Figure 24 is smaller.

To assess the homogeneity of the blend operations, the relative standard deviation (RSD) was computed for each step injection experiments (Figure 25). RSD is also known

as the coefficient of variability and is the most common mixing index used in the pharmaceutical industry. In continuous blending, RSD is temporally assesse. In batch blending, it is spatially assessed as samples are collected in different locations of the blender.

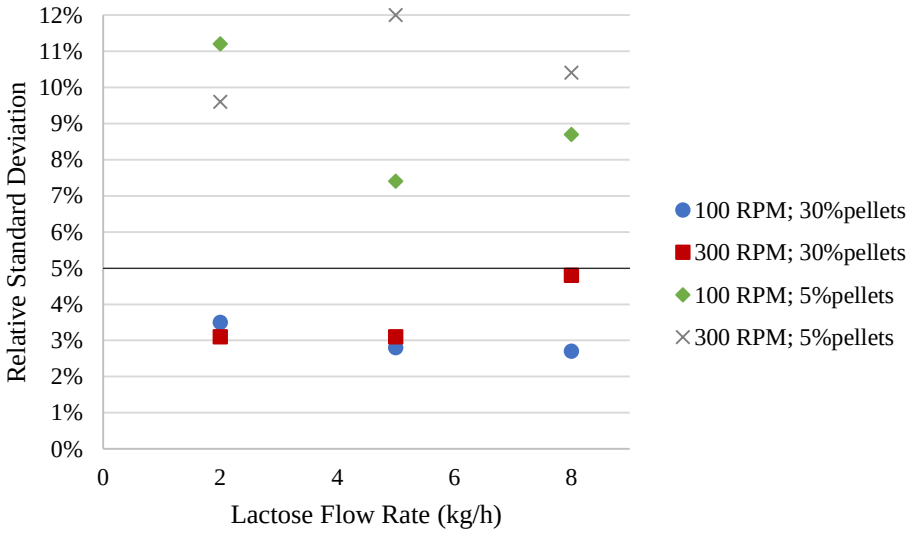


Figure 25: Relative standard deviation from a 10 minutes continuous blending experiments as a function of operation parameters flow rate and rotation rate. The black line states the RSD threshold defined by European Pharmacopoeia.

The RSD characterizes the uniformity of each mixture. When RSD is smaller, concentrations of the individual samples are closer to the mean concentration, which indicates better blend uniformity, thus better mixer performance. In Figure 25, the RSD for each mixing experiment is compared to the threshold value defined by FDA for powder blends quality assessment (FDA, 2003). The RSD of all individual results should be $\leq$ 5.0 percent.

As observed in Figure 25, satisfactory uniformity of dose across the samples is not reached when 5% of pellets were used. This is because RSD is the standard deviation of samples' pellets content expressed as a percentage of the mean. In this case, the mean value is very small (around 5%). So, even if the standard deviation values are acceptable, the resulting RSD value is high.

Regarding the six experiments in which 30% of pellets were used, all satisfy the homogeneity criteria. There is a slight decreasing of blend homogeneity when flow rate increased, for the same rotation rate of 100 rpm. This behavior was not observed when rotation rate was set for 300 rpm. Here, the blend quality is the same for 2 kg/h and 5 kg/h and decreased when increasing flow rate to 8kg/h.

The smallest RSD value was obtained with a high flow rate and low rotational speed, more exactly when the process was at 8 kg/h of lactose, 3.43 kg/h of pellets and 100 rpm. Relating with previous section results, this experimental conditions correspond to a broad RTD curve. A high hold-up mass and an intermediate mean residence time of pellets inside the blender (57 seconds) seemed to be the optimal tested conditions that allowed pellets and lactose to undergo the optimal quantity of blade revolutions to achieve a good blend homogeneity. In these conditions, the MCV corresponds to an intermediate value (0.43, having in mind that MCV spans between 0 and 1). As a result, in these conditions it was not necessary an extensive axial dispersion to produce a good quality mixture. The main objective of axial mixing is to smooth out fluctuations introduced by the feeding system. Usually, feeders are more accurate when using high flow rates. Perhaps, another reason for this good blend homogeneity is the higher feeding accuracy at high throughputs and the axial mixing is shorter.

On the opposite side, at 8kg/h and 300 rpm the obtained RSD value is very close to the defined threshold. Here, the lowest mean residence time was observed over all the experimental conditions. On average, a pellet particle spends 33 seconds inside the blender under these conditions. This fact, associated to a low blender fill level, doesn't give sufficient time for pellets to mix within lactose (which has a low residence time, too).

Martínez et al. (2013), Portillo, Ierapetritou, & Muzzio (2009) and Williams & Rahman (1970) achieved improved blend uniformity at lower rotation rates. However, they assign this result to the longer residence time obtained in those conditions. The same results were obtained here, but correspond to an intermediate mean residence time of pellets.

Portillo et al. (2008) found that the most dispersed RTD corresponds to the worst mixing in a convective continuous mixer, due to the low number of blade passes experienced by the powder as it travels along the mixer axis. In contrast, the present work revealed that the best mixing performance is related to a broad RTD curve.

Chapter 6 – Conclusions

In this work it was studied the flow behavior and the mixing performance of a Modulomix continuous powder mixer (by Hosokawa Micron), using a mixture of pellets made of povidone polymer and lactose monohydrate.

The first experimental work performed was focused on the development of an on-line method using near-infrared spectroscopy to monitor the continuous mixing process, by measuring the pellets concentration at the outlet of the equipment. NIRS had already been successfully applied and reported in the literature as accurate when monitoring a continuous mixing processes. At least two studies were published in this field, more precisely to predict the API concentration in the outflowing powder blend and thus evaluate the blend homogeneity. Although, in this work, the efforts made using NIRS to real-time monitor the pellet concentration at the outlet of the continuous blender were abandoned in the phase of the calibration model development. Since it is optimal to perform calibration under the same conditions as the blending measurements, two laboratory setups were designed to reproduce as faithfully as possible the feasible ways to collect the on-line spectra at the blender outlet. The PLS models obtained had high errors when predicting pellets concentration, hence they should not be used in residence time distribution and homogeneity studies, since pellets content should be accurately measured over a broad range of values. The appearance of erroneous spectra might be related to the fact that pellets were completely covered by lactose powder. Additionally, it is known that there are differences and emerging issues when measuring moving samples, in contrast to static powders. The motion of particles produces changes in the density and distribution of the voids, thus influencing the NIR measurements. For further work, one suggests the usage of pellets containing an API with a characteristic peak in the NIR region, in their core or in the coating.

Consequently, continuous blender's residence time distributions and homogeneity measurements were performed with an off-line particle size analysis.

Blender's rotation rate and feeding rate are the most important process variables in a continuous mixing process, hence the importance of understanding how their manipulation changes the flow behavior inside the blender or the blend homogeneity.

The effect of flow rate and blender rotation rate on materials' flow behavior within the continuous mixer was characterized using: residence time distributions, mean residence time of pellets, mean residence time of lactose, mean centered variance, hold-

up mass, shear intensity and powder hold-up measurements. For this, pulse injection experiments were performed. The blender performance was characterized by the relative standard deviation. Here, step injection experiments were performed. Both RTD and RSD were measured as a function of impeller rotation rate and flow rate, using two different proportions of pellets and lactose.

Regarding the flow behavior characterization, it can be summarized as follows. The hold-up mass decreases when increasing the rotation rate and it increases when increasing the bulk feeding rate. At low throughputs, the mean residence time of pellets increased when increasing the rotation rate. In these conditions, centrifugal forces are predominant inside the blender. Thus, the incoming stream (only 2 kg/h) does not have sufficient strength to push pellets to the end of the blender, so, they spend more time having radial mixing instead of moving in the axial direction, resulting in a higher mean residence time. The existence of back mixing can be questioned and could equally explain the high mean residence time of pellets in the referred operational conditions. The mean centered variance (extension of axial mixing) and the number of blade passes (measurement of shear intensity) increases when blender's rotation rate increases. No particular trend was observed when changing flow rate.

Rotation rate was found to be the most significant process parameter affecting mix homogeneity and the low rotational speed showed the best mixing, as reflected by the smaller RSD obtained. The exact experimental conditions that led to it were 8 kg/h lactose flow rate, 3.43 kg/h pellets flow rate and 100 rpm. This result is justified by the intermediate mean residence time of pellets inside the blender under these conditions. Thus, pellets and lactose spend enough time inside the blender to suffer the appropriate quantity of blade revolutions to achieve a good blend homogeneity. Another reason for this good blend homogeneity is the higher feeding accuracy at high throughputs.

The differences observed between this work's results and other described in the literature might be at the level of the different particles used. All of the continuous mixing studies performed in the pharmaceutical area addressed fine powders and mixes with similar particle size. Continuous mixing of pharmaceutical pellets has not been described yet in literature.

For segregating blends such as the one used in this study, it is suggested that the RTD measurements are performed for lactose using the same experimental protocol used for studying pellets' RTD. This is due to the fact that they seem to have different residence time inside the blender. Thus, the mean residence time of lactose calculated as the ratio

of hold-up mass and bulk feed rate maybe is not enough. The RTD for the lactose should be investigated using tracer experiments. This tracer should have a particle size similar to lactose or it should be a smaller and cohesive powder in such a way that its particles adhere to lactose and coat it, thus having the same flow behavior and residence time as lactose.

It should be beared in mind that segregation can occur after blending. Despite the great significance of knowing how different process parameters influence the blender performance, the final drug product might not achieved the desired homogeneity if segregation points beyond blending are not handled. Segregation can occur during powder transfer between the continuous mixer and the tablet press and in the tablet press hopper or dies due to vibrations. It is even more critical with a mixture containing pellets, having in account their free flowing features.

During a continuous manufacturing process, the flow rate through the blender is typically determined by the capacity of other process components (for example the extruder or the tablet press). Thus it is important that the kind of studies performed here are repeated latter in the manufacturing line development, depending on the desired throughput. A flow rate of 2 kg/h is a too low flow rate for a continuous production line.

This work improved the knowledge about how pellets behave in a continuous mixer under different process parameters and gave some insight about the better conditions to achieve a homogenous blend. Nevertheless, the results and conclusions achieved here might not be applicable if using other pellets. Pellets containing an API in their core and some additional excipients will have different density, which is a big enough factor to induce a different mixing flow behavior.

References

Abdul, S., Chandewar, A. V., & Jaiswal, S. B. (2010). A flexible technology for modified-release drugs: Multiple-unit pellet system (MUPS). *Journal of Controlled Release*, *147*(1), 2–16.

Allison, G., Cain, Y. T., Cooney, C., Garcia, T., Bizjak, T. G., Holte, O., … Zezza, D. (2014). Regulatory and quality considerations for continuous manufacturing. *Discussion at the International Symposium on Continuous Manufacturing of Pharmaceuticals*.

Bakeev, K. (2005). *Process Analytical Technology*. Blackwell Publishing.

Barnes, R. J., Dhanoa, M. S., & Lister, S. J. (1989). Standard normal variate transformation and de-trending of near-infrared diffuse reflectance spectra. *Applied Spectroscopy*, *43*(5), 772–777.

Beaudry, J. P. (1948). Blender efficiency. *Chemical Engineering*, 112–113.

Berthiaux, H., Marikh, K., & Gatumel, C. (2008). Continuous mixing of powder mixtures with pharmaceutical process constraints. *Chemical Engineering and Processing*, *47*, 2315–2322.

Blanco, M., Alcal, M., Menezes, J. C., Felizardo, P. M., Garrido, A., Dolores, P., … Romañach, R. J. (2012). Near-infrared Spectroscopy in Laboratory and Process Analysis. In *Encyclopedia of Analytical Chemistry* (pp. 1–46).

Breitenbach, J. (2002). Melt extrusion: from process to drug delivery technology. *European Journal of Pharmaceutics and Biopharmaceutics*, *54*(2), 107–117.

Burns, D. A., & Ciurczak, E. W. (2007). *Handbook of Near-Infrared Analysis* (3rd Editio). CRC Press.

Byrn, S., Futran, M., Thomas, H., Jayjock, E., Maron, N., Meyer, R. F., … Trout, B. L. (2015). Achieving continuous manufacturing for final dosage formation: Challenges and how to meet them. *Journal of Pharmaceutical Sciences*, *104*(3), 792–802.

Chatterjee, S. (2012). FDA Perspective on Continuous Manufacturing. *IFPAC Annual Meeting*. Retrieved from http://www.fda.gov/downloads/AboutFDA/Centers Offices/OfficeofMedicalProductsandTobacco/CDER/UCM341197.pdf

Cullen, P., Romañach, R., Abatzoglou, N., & Rielly, C. (2015). Continuous Powder Mixing. In *Pharmaceutical Blending and Mixing* (pp. 101–127).

Danckwerts, P. V. (1952). The definition and measurement of some characteristics of mixtures. *Applied Scientific Research, Section A*, *3*(4), 279–296.

Danckwerts, P. V. (1953). Continuous flow systems. Distribution of residence times. *Chemical Engineering Science*, *2*, 3857–3866.

De Brabander, C., Vervaet, C., & Remon, J. P. (2003). Development and evaluation of sustained release mini-matrices prepared via hot melt extrusion. *Journal of Controlled Release*, *89*(2), 235–247.

Engisch, W. E., & Muzzio, F. J. (2012). Method for characterization of loss-in-weight feeder equipment. *Powder Technology*, *228*, 395–403.

Ervasti, T., Simonaho, S.-P., Ketolainen, J., Forsberg, P., Fransson, M., Wikström, H., … Abrahmsén-Alami, S. (2015). Continuous manufacturing of extended release tablets via powder mixing and direct compression. *International Journal of Pharmaceutics*, *495*(1), 290–301.

European Pharmacopoeia, 7.0. (2011). Chapter 2.9.36 - Powder Flow, *Volume 1*, 308–311.

FDA. (2003). Guidance for Industry. Powder blends and finished dosage units - Stratified In-Process dosage unit sampling and assessment.

FDA. (2004). Guidance for Industry PAT — A Framework for Innovative Pharmaceutical Development, Manufacuring, and Quality Assurance. Retrieved from http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm070305.pdf

Fogler, H. S. (2006). Distributions of residence times of chemical reactors. In *Elements of Chemical Reaction Engineering* (4th ed., pp. 867–944). Pearson Education, Inc.

Follonier, N., Doelker, E., & Cole, E. T. (1995). Various ways of modulating the release of diltiazem hydrochloride from hot-melt extruded sustained release pellets prepared using polymeric materials. *Journal of Controlled Release*, *36*(3), 243–250.

Fonteyne, M., Vercruysse, J., De Leersnyder, F., Van Snick, B., Vervaet, C., Remon, J. P., & De Beer, T. (2015). Process Analytical Technology for continuous manufacturing of solid-dosage forms. *Trends in Analytical Chemistry*.

Gao, Y., Muzzio, F., & Ierapetritou, M. (2011). Characterization of feeder effects on continuous solid mixing using Fourier series analysis. *AIChE Journal*, *57*(5), 1144–1153.

Gao, Y., Vanarase, A., Muzzio, F., & Ierapetritou, M. (2011). Characterizing continuous powder mixing using residence time distribution. *Chemical Engineering Science*, *66*(3), 417–425.

Gericke, H. (1993). Different methods of batch and continuous mixing of solids. *Bulk Solids Handling*, *13*(1).

Harnby, N., Edwards, M. F., & Nienow, A. W. (1992). *Mixing in the process industries*. *Butterworth-Heinemann* (2nd ed.).

Harwood, C. F., Walanski, K., Luebcke, E., & Swanstorm, C. (1975). The performance of continuous mixers for dry powders. *Powder Technology*, *11*(3), 289–296.

Hickey, A. J., & Ganderton, D. (2010). Chapter 13: Mixing. In *Pharmaceutical Process Engineering* (2nd Editio, pp. 155–167). Informa Healthcare.

Hosokawa Micron, B. V. (2014). *Batch & continuous mixing technologies brochure*. Retrieved from http://www.vekamaf.com/documents/54/Hosokawa Micron mixing technology brochure.pdf

Hou, Q. F., Dong, K. J., & Yu, A. B. (2014). DEM study of the flow of cohesive particles in a screw feeder. *Powder Technology*, *256*, 529–539.

International Conference on Harmonisation. (2009). ICH Harmonised Tripartite Guideline Q8(R2), Pharmaceutical Development.

Jawahar, N., & Anilbhai, P. H. (2012). Multi unit particulates systems (MUPS): A novel pellets for oral dosage forms. *Journal of Pharmaceutical Sciences and Research*, *4*(9), 1915–1923.

Köhler, U., List, J., & Witt, W. (2007). Comparison of laser diffraction and image analysis under identical dispersing conditions. In *PARTEC - International Congress for Particle Technology*. Nürnberg.

Lacey, P. M. C. (1954). Developments in the theory of particle mixing. *Journal of Applied Chemistry*, *4*(5), 257–268.

Lai, C. K., Holt, D., Leung, J. C., Cooney, C. L., Raju, G. K., & Hansen, P. (2001). Real time and noninvasive monitoring of dry powder blend homogeneity. *AIChE Journal*, *47*(11), 2618–2622.

Laurent, B. F. C., Bridgwater, J., & Parker, D. J. (2000). Motion in a particle bed agitated by a single blade. *AIChE Journal*, *46*(9), 1723–1734.

Laurent, B. F. C., Bridgwater, J., & Parker, D. J. (2002). Convection and segregation in a horizontal mixer. *Powder Technology*, *123*(1), 9–18.

Lavine, B. K. (2000). Chemometrics. *Analytical Chemistry*, *72*(12), 91–97.

Marikh, K., Berthiaux, H., Gatumel, C., Mizonov, V., & Barantseva, E. (2008). Influence of stirrer type on mixture homogeneity in continuous powder mixing: A model case and a pharmaceutical case. *Chemical Engineering Research and Design*, *86*(9), 1027–1037.

Marikh, K., Berthiaux, H., Mizonov, V., & Barantseva, E. (2005). Experimental study of the stirring conditions taking place in a pilot plant continuous mixer of particulate solids. *Powder Technology*, *157*(1-3), 138–143.

Marikh, K., Berthiaux, H., Mizonov, V., Barantseva, E., & Ponomarev, D. (2006). Flow analysis and Markov chain modelling to quantify the agitation effect in a continuous powder mixer. *Chemical Engineering Research and Design*, *84*(11), 1059–1074.

Martínez, L., Peinado, A., Liesum, L., & Betz, G. (2013). Use of near-infrared spectroscopy to quantify drug content on a continuous blending process: Influence of mass flow and rotation speed variations. *European Journal of Pharmaceutics and Biopharmaceutics*, *84*(3), 606–615.

McKenzie, P., Kiang, S., Tom, J., Rubin, A. E., & Futran, M. (2006). Can Pharmaceutical Process Development Become High Tech? *AIChE Journal*, *52*(12), 3990–3994.

MEGGLE, E. & T. (2014). *Technical brochure Tablettose®*. Retrieved from http://www.meggle-pharma.com/pt/documents/upload/86/tablettose.pdf

Mehta, K. A., Rekhi, G. S., & Parikh, D. M. (2005). Extrusion/Spheronization as a Granulation Technique. In *Handbook of Pharmaceutical Granulation Technology* (pp. 333–363).

Muzzio, F. J., Alexander, A., Goodridge, C., Shen, E., & Shinbrot, T. (2004). Solids Mixing. In *Handbook of Industrial Mixing. Science and Practice* (pp. 887–985).

Nauman, E. (2008). Residence time theory. *Industrial & Engineering Chemistry Research*, *47*(10), 3752 – 3766.

Nowak, S. (2010). Volumetric and gravimetric feeders: Ways to optimize performance. *Powder and Bulk Enginnering*.

Ottino, J. M., & Khakhar, D. V. (2000). Mixing and segregation of granular materials. *Annual Review of Fluid Mechanics*, *32*, 55–91.

Pernenkil, L. (2008). *Continuous blending of dry pharmaceutical powders*. PhD Dissertation. Massachusetts Institute of Technology.

Pernenkil, L., & Cooney, C. L. (2006). A review on the continuous blending of powders. *Chemical Engineering Science*, *61*(2), 720–742.

Plumb, K. (2005). Continuous processing in the pharmaceutical industry: Changing the mind set. *Chemical Engineering Research and Design*, *83*(A6), 730–738.

Portillo, P. M., Ierapetritou, M. G., & Muzzio, F. J. (2008). Characterization of continuous convective powder mixing processes. *Powder Technology*, *182*(3), 368–378.

Portillo, P. M., Ierapetritou, M. G., & Muzzio, F. J. (2009). Effects of rotation rate, mixing angle, and cohesion in two continuous powder mixers—A statistical approach. *Powder Technology*, *194*(3), 217–227.

Portillo, P. M., Muzzio, F. J., & Ierapetritou, M. G. (2007). Hybrid DEM-compartment modeling approach for granular mixing. *AIChE Journal*, *53*(1), 119–128.

Portillo, P. M., Vanarase, A. U., Ingram, A., Seville, J. K., Ierapetritou, M. G., & Muzzio, F. J. (2010). Investigation of the effect of impeller rotation rate, powder flow rate, and cohesion on powder flow behavior in a continuous blender using PEPT. *Chemical Engineering Science*, *65*(21), 5658–5668.

Poux, M., Fayolle, P., Bertrand, J., Bridoux, D., & Bousquet, J. (1991). Powder mixing: Some practical rules applied to agitated systems. *Powder Technology*, *68*(3), 213–234.

Reddy, S., Das, P., Das, H., & Ghosh, A. (2011). MUPS (Multiple Unit Pellet System) Tablets – A Brief Review. *Journal of Pharmaceutical and Biomedical Sciences*, *12*(12), 1–5.

Rinnan, Åsmund, Berg, F. van den, & Engelsen, S. B. (2009). Review of the most common pre-processing techniques for near-infrared spectra. *Trends in Analytical Chemistryrends in Analytical Chemistry*, *28*(10), 1201–1222.

Roggo, Y., Chalus, P., Maurer, L., Lema-Martinez, C., Edmond, A., & Jent, N. (2007). A review of near infrared spectroscopy and chemometrics in pharmaceutical technologies. *Journal of Pharmaceutical and Biomedical Analysis*, *44*, 683–700.

Sarkar, A., & Wassgren, C. (2010). Continuous blending of cohesive granular material. *Chemical Engineering Science*, *65*(21), 5687–5698.

Sarkar, A., & Wassgren, C. R. (2009). Simulation of a continuous granular mixer: Effect of operating conditions on flow and mixing. *Chemical Engineering Science*, *64*(11), 2672–2682.

Schaber, S. D., Gerogiorgis, D. I., Ramachandran, R., Evans, J. M. B., Barton, P. I., & Trout, B. L. (2011). Economic Analysis of Integrated Continuous and Batch Pharmaceutical Manufacturing: A Case Study. *Industrial & Engineering Chemistry Research*, *50*(17), 10083–10092.

Scheibelhofer, O., Balak, N., Koller, D. M., & Khinast, J. G. (2013). Spatially resolved monitoring of powder mixing processes via multiple NIR-probes. *Powder Technology*, *243*, 161–170.

Simonaho, S.-P., Ketolainen, J., Ervasti, T., Toiviainen, M., & Korhonen, O. (2016). Continuous manufacturing of tablets with PROMIS-line – Introduction and case studies from continuous feeding, blending and tableting. *European Journal of Pharmaceutical Sciences*.

Sudah, O. S., Chester, A. W., Kowalski, J. A., Beeckman, J. W., & Muzzio, F. J. (2002). Quantitative characterization of mixing processes in rotary calciners. *Powder Technology*, *126*(2), 166–173.

Treffer, D., Wahl, P. R., Hörmann, T. R., Markl, D., Schrank, S., Jones, I., … Khinast, J. G. (2014). In-line implementation of an image-based particle size measurement tool to monitor hot-melt extruded pellets. *International Journal of Pharmaceutics*, *466*(1-2), 181–189.

Vanarase, A. U., Alcalà, M., Jerez Rozo, J. I., Muzzio, F. J., & Romañach, R. J. (2010). Real-time monitoring of drug concentration in a continuous powder mixing process using NIR spectroscopy. *Chemical Engineering Science*, *65*(21), 5728–5733.

Vanarase, A. U., & Muzzio, F. J. (2011). Effect of operating conditions and design parameters in a continuous powder mixer. *Powder Technology*, *208*(1), 26–36.

Vogeleer, J. (2014). Solving Segregation Challenges in MUPS Production. Retrieved November 1, 2015, from http://www.gea.com/global/en/stories/mups-production.jsp

Wagner, K. G., Krumme, M., Beckert, T. E., & Schmidt, P. C. (2000). Development of disintegrating multiple-unit tablets on a high-speed rotary tablet press. *European Journal of Pharmaceutics and Biopharmaceutics*, *50*(2), 285–291.

Wagner, K. G., Krumme, M., & Schmidt, P. C. (1999). Investigation of the pellet-distribution in single tablets via image analysis. *European Journal of Pharmaceutics and Biopharmaceutics*, *47*(1), 79–85.

Wahl, P. R., Fruhmann, G., Sacher, S., Straka, G., Sowinski, S., & Khinast, J. G. (2014). PAT for tableting: Inline monitoring of API and excipients via NIR spectroscopy. *European Journal of Pharmaceutics and Biopharmaceutics*, *87*(2), 271–278.

Wahl, P. R., Treffer, D., Mohr, S., Roblegg, E., Koscher, G., & Khinast, J. G. (2013). Inline monitoring and a PAT strategy for pharmaceutical hot melt extrusion. *International Journal of Pharmaceutics*, *455*(1-2), 159–168.

Williams, J. C. (1976). Continuous mixing of solids. A review. *Powder Technology*, *15*, 237–243.

Williams, J. C., & Rahman, M. A. (1970). The continuous mixing of particulate solids. *Journal of the Society of Cosmetic Chemists*, *36*(1070), 3 – 36.

Williams, J. C., & Rahman, M. a. (1972). Prediction of the performance of continuous mixers for particulate solids using residence time distributions Part I. Theoretical. *Powder Technology*, *5*(2), 87–92.

Witt, W., Köhler, U., & List, J. (2004). Direct imaging of very fast particles opens the

application of the powerful (dry) dispersion for size and shape characterization. In *PARTEC - International Congress for Particle Technology*. Nürnberg.

Ziegler, G. R., & Aguilar, C. A. (2003). Residence time distribution in a co-rotating, twin-screw continuous mixer by the step change method. *Journal of Food Engineering*, *59*(2-3), 161–167.

Appendices

Appendix 1: Pellets' particle size analysis report by QICPIC.

Sympatec GmbH
System-Partikel-Technik

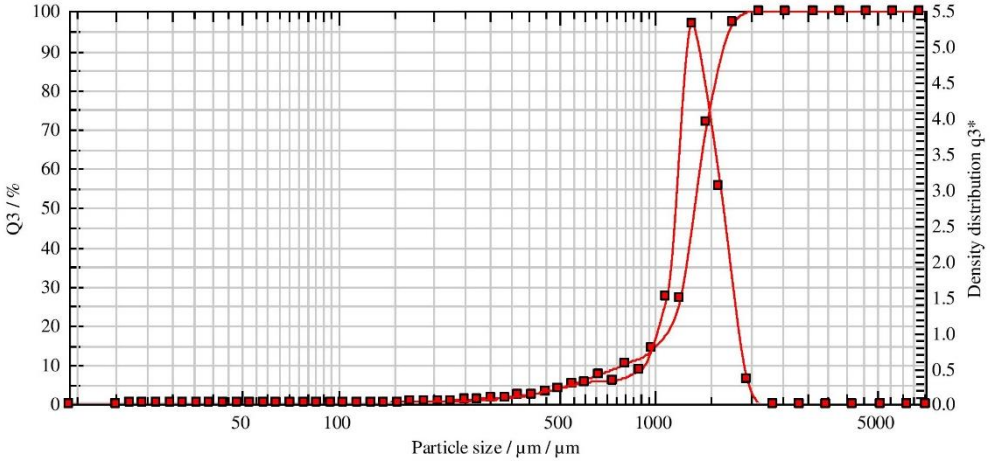
QICPIC-Partikelgrößenanalyse
WINDOX 5

QICPIC (QP0112) & RODOS, 2.00 63.0 mm - M8 (20...6820µm)
Ana Martins **2016-02-04, 14:27:57**,656

x_{10} = 793,66 +/- 0,00 µm	**x_{50} = 1318,04 +/- 0,00 µm**	**x_{90} = 1662,61 +/- 0,00 µm**
x_{16} = 1007,64 +/- 0,00 µm	x_{84} = 1590,38 +/- 0,00 µm	x_{99} = 1991,20 +/- 0,00 µm
VMD = 1276,62 µm +/- 0,00 µm		C_{opt} = 0,23 +/- 0,00 % [0,00 %]
SMD = 1075,54 µm +/- 0,00 µm	RRSB d' = 1412,11 µm	RRSB n = 4,03
Partikelanzahl = 224583		

x_{90}/x_{10} = 2,09	Monosized < 1,02	Medium 1,5 - 4
Polydispersity index: 0,25	Ultra narrow 1,02 - 1,05	Broad 4 - 10
StandardDeviation of the PSD: 332,57 µm	Narrow 1,05 - 1,5	Very broad > 10

Konditionen:		**Benutzerparameter:**
Produkt:	Ana Martins	User: Piller, Martins
Auswertung:	EQPC (5.6.0.0)	Sample Sescription: Pellets pure
Trigger:	Standard400Hz	Measurement Number: 1,00
Disp.Meth.:	Standard_Dry_10mm	:



Verteilungssumme mit Standardabweichung

x_3/µm	Q_3/%	SQ_3/%abs	x_0/µm	Q_3/%	SQ_3/%abs	x_0/µm	Q_3/%	SQ_3/%abs
20,00	0,00	0,00	206,13	0,72	0,00	2124,39	100,00	0,00
24,29	0,00	0,00	250,36	1,02	0,00	2580,23	100,00	0,00
29,50	0,01	0,00	304,08	1,42	0,00	3133,89	100,00	0,00
35,84	0,01	0,00	369,32	2,07	0,00	3806,35	100,00	0,00
43,52	0,02	0,00	448,57	3,16	0,00	4623,11	100,00	0,00
52,86	0,03	0,00	544,83	4,99	0,00	5615,12	100,00	0,00
64,21	0,06	0,00	661,73	7,50	0,00	6820,00	100,00	0,00
77,98	0,10	0,00	803,73	10,19	0,00	7307,77	100,00	0,00
94,72	0,16	0,00	976,19	14,12	0,00			
115,04	0,25	0,00	1185,65	26,66	0,00			
139,73	0,36	0,00	1440,07	71,51	0,00			
169,71	0,52	0,00	1749,08	97,18	0,00			

Appendix 2: Lactose Tablettose 70® particle size analysis report by QICPIC.

Sympatec GmbH
System-Partikel-Technik

QICPIC-Partikelgrößenanalyse
WINDOX 5

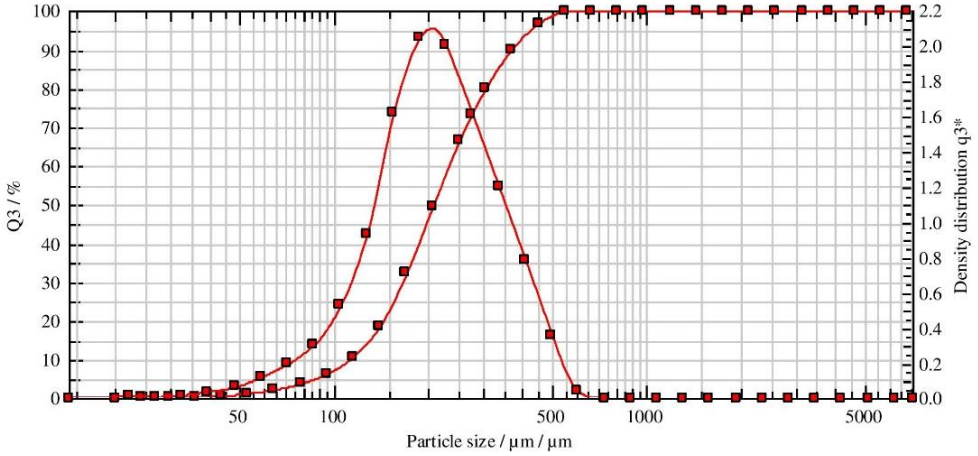
QICPIC (QP0112) & RODOS, 2.00 63.0 mm - M8 (20...6820µm)
Ana Martins **2016-02-04, 14:30:17**,984

x_{10} = 111,82 +/- 0,00 µm	**x_{50} = 207,45 +/- 0,00 µm**	**x_{90} = 368,82 +/- 0,00 µm**
x_{16} = 131,64 +/- 0,00 µm	x_{84} = 330,10 +/- 0,00 µm	x_{99} = 522,56 +/- 0,00 µm
VMD= 226,69 µm +/- 0,00 µm		C_{opt} = 0,44 +/- 0,00 % [0,00 %]
SMD = 179,18 µm +/- 0,00 µm	RRSB d' = 249,22 µm	RRSB n = 2,47
Partikelanzahl = 3083568		

x_{90}/x_{10} = 3,30
Polydispersity index: 0,49
StandardDeviation of the PSD: 101,74 µm

Monosized < 1,02	Ultra narrow 1,02 - 1,05	Narrow 1,05 - 1,5
Medium 1,5 - 4	Broad 4 - 10	Very broad > 10

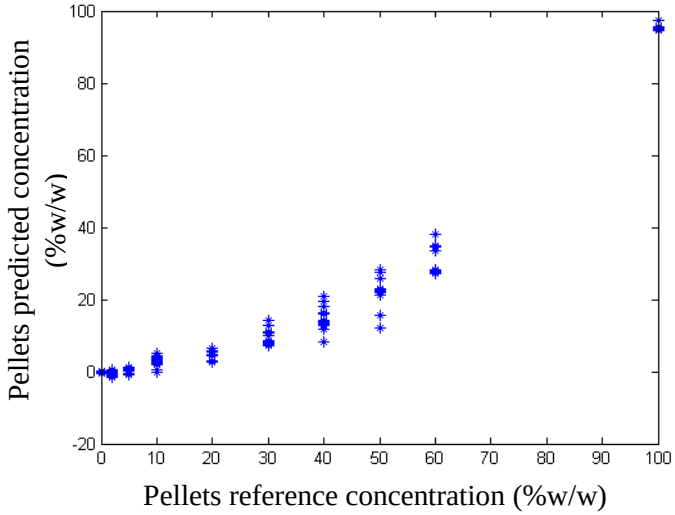
Konditionen:		**Benutzerparameter:**
Produkt:	Ana Martins	User: Piller, Martins
Auswertung:	EQPC (5.6.0.0)	Sample Sescription: Tablettose 70
Trigger:	Standard400Hz	Measurement Number: 1,00
Disp.Meth.:	Standard_Dry_10mm	:



Verteilungssumme mit Standardabweichung

x_3/µm	Q_3/%	SQ_3/%abs	x_0/µm	Q_3/%	SQ_3/%abs	x_0/µm	Q_3/%	SQ_3/%abs
20,00	0,00	0,00	206,13	49,49	0,00	2124,39	100,00	0,00
24,29	0,09	0,00	250,36	66,38	0,00	2580,23	100,00	0,00
29,50	0,16	0,00	304,08	79,97	0,00	3133,89	100,00	0,00
35,84	0,29	0,00	369,32	90,08	0,00	3806,35	100,00	0,00
43,52	0,58	0,00	448,57	96,68	0,00	4623,11	100,00	0,00
52,86	1,10	0,00	544,83	99,70	0,00	5615,12	100,00	0,00
64,21	2,10	0,00	661,73	100,00	0,00	6820,00	100,00	0,00
77,98	3,72	0,00	803,73	100,00	0,00	7307,77	100,00	0,00
94,72	6,27	0,00	976,19	100,00	0,00			
115,04	10,70	0,00	1185,65	100,00	0,00			
139,73	18,58	0,00	1440,07	100,00	0,00			
169,71	32,22	0,00	1749,08	100,00	0,00			

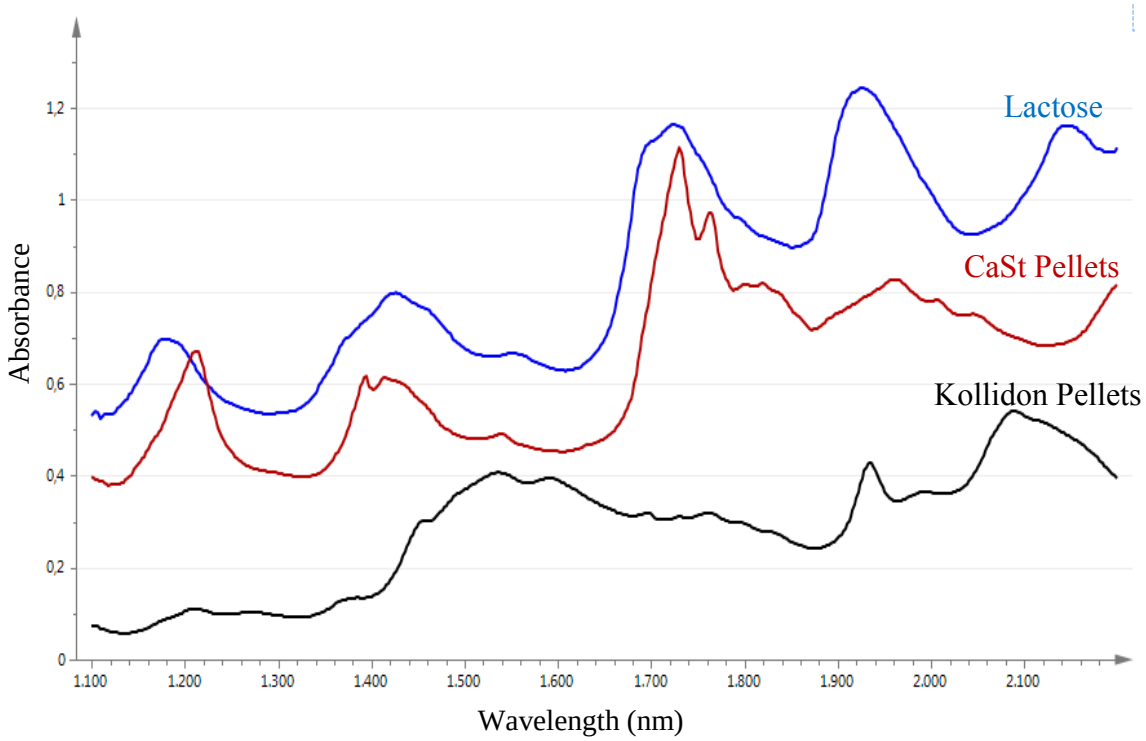
Appendix 3: Multivariate curve resolution result, using spectra acquired in the rotating plate 1 experiment.



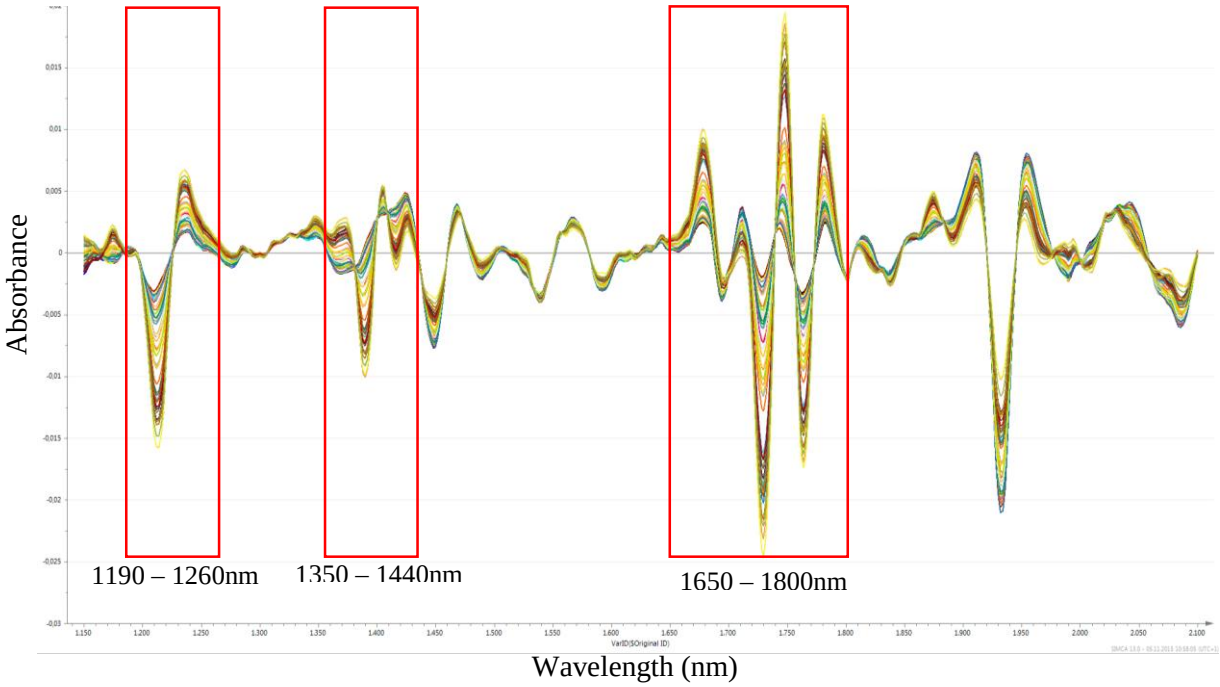
Appendix 3: Visual appearance of a mixture of 50% (w/w) pellets and lactose.

Appendix 5: Visual appearance of calcium stearate pellets.

Appendix 6: Comparison between reflectance intensity of pure Kollidon pellets, pure calcium stearate pellets and pure lactose monohydrate.



Appendix 7: Calibration samples' spectra for rotating plate experiment using CaSt pellets, after pretreatment with SNV and 2nd derivative. The marked area shows the spectral ranges selected for building the PLS model.



Appendix 8: Observed vs predicted plot for the PLS model developed with CaSt pellets.