TPLS AS PREDICTIVE PLATFORM FOR TWIN-SCREW WET GRANULATION PROCESS AND FORMULATION DEVELOPMENT

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Abbreviations: API, Active Pharmaceutical Ingredient; CQA, critical quality attribute L/S, liquid-to-solid; MCC, microcrystalline cellulose; MFR, mass feed rate; PCA, Principal Component Analysis; PLS, Partial Least Squares; TPLS, T-shaped partial least squares;

**ABSTRACT**

In recent years, the interest in continuous manufacturing techniques, such as twin-screw wet granulation, has increased. However, the understanding of the influence of the combination of raw material properties and process settings upon the granule quality attributes is still limited. In this study, a T-shaped partial least squares (TPLS) model was developed to link raw material properties, the ratios in which these raw materials were combined and the applied process parameters for the twin-screw wet granulation process with the granule quality attributes. In addition, the predictive ability of the TPLS model was used to find a suitable combination of formulation composition and twin-screw granulation process settings for a new API leading to desired granule quality attributes. Overall, this study helped to better understand the link between raw material properties, formulation composition and process settings on granule quality attributes. Moreover, as TPLS can provide a reasonable starting point for formulation and process development for new APIs, it can reduce the experimental development efforts and consequently the consumption of expensive (and often limited available) new API.

# Introduction

Twin-screw wet granulation is the most studied continuous wet granulation technique (Vervaet and Remon, 2005). Generally, the granules’ critical quality attributes (CQAs) depend on the properties of the selected raw materials, the ratio in which these raw materials are combined and the applied process settings during granulation. Understanding how the combination of these three aspects affects granule quality is not only an advantage during manufacturing, it is extremely beneficial during the formulation and continuous twin-screw wet granulation process design for a new API (Garcia-Munoz, 2014). Especially when limited amounts of expensive API are available during the early drug product development stages (Lee et al., 2015; Van Snick et al., 2018).

Multiple studies have investigated the effect of twin-screw granulation process parameters – such as liquid-to-solid (L/S) ratio, mass feed rate (MFR) and screw speed – upon granule quality (Dhenge et al., 2010, 2011, 2012a; Djuric and Kleinebudde, 2010; Fonteyne et al., 2015; Meier et al., 2017; Portier et al., 2020b; Vanhoorne et al., 2016; Vercruysse et al., 2012, 2015; Verstraeten et al., 2017). Generally, L/S ratio was the most influencing process parameter. However, contradictory results were often seen for the effect of MFR and screw speed upon the granules’ CQAs, due to the different formulations under study. Others have investigated the effect of raw materials properties on granule quality (Fonteyne et al., 2015, 2014; Hwang et al., 2019; Lute et al., 2018). However, these investigations were only limited to one ingredient at a time, because different compositions of studied formulations require different process settings, resulting in a complicated data analysis (Thompson, 2015).

Willecke et al. (Willecke et al., 2018, 2017) were able to study more divergent formulations by investigating the impact of excipient characteristics in a two-part study. In the first part, an extensive raw material characterization was performed on the excipients (fillers and binders) prior to Principal Component Analysis (PCA). Subsequently, the large number of the material properties of the excipients were reduced by identifying representative overarching properties from the PCA (Willecke et al., 2017). In the second part, different excipients were selected representing these overarching properties. Then, after granulation and tableting experiments, the influence of the overarching properties of binder and filler upon granule and tablet quality was studied (Willecke et al., 2018). The impact of API properties on granule quality was however not investigated. More recently, Portier et al. (Portier et al., 2020b) investigated the impact of granulation process settings and screw configuration on granulation behaviour of different formulations. These formulations varied in API content, API type and filler type (i.e., lactose or lactose/microcrystalline cellulose (MCC) (1:1)). The study showed that lactose in combination with MCC resulted in improved process robustness. For both the study of Willecke et al. and Portier et al., a one-on-one comparison of the granules’ CQAs of different formulations was unfortunately still impeded due to different L/S ratios. This shortcoming of aforementioned studies can be overcome using T-shaped partial least squares (TPLS), a method developed by Munoz et al. (Garcia-Munoz, 2014). TPLS allows to investigate the individual and combined effect of formulation and process parameters on granule quality. In a case study, the author was able to determine the most influencing process parameters and raw material properties upon dissolution time after encapsulation of granules. By understanding the lot-to-lot variability of the different ingredients, it was possible to selectively combine certain lots of the different ingredients to minimize the variability in final product quality.

TPLS, being a regression method, has also the ability to predict the product quality attributes for given raw material properties, blend ratio’s and process settings. Hence, the prediction of the optimal combination of formulation composition and twin-screw process parameters for a new API based on its critical material properties leading to desired granule quality attributes is possible. This is very beneficial as it could reduce the experimental effort, the consumption of the expensive API and the development time during early drug product development.

The goal of current study was to better understand the link between raw material properties, formulation composition and process settings on granule quality attributes, and to develop a TPLS model allowing the formulation and twin-screw granulation process development for new APIs (with limited experimental efforts). The study consisted of three major parts. In the first part, a TPLS model was established for twin-screw granulation. First, an extensive raw material database was developed by determining multiple raw material characteristics of excipients and APIs. Next, APIs and excipients with varying raw material properties were selected based on PCA. Subsequently, these selected APIs (10, 40 or 70 % API content) and excipients were combined to obtain very divergent powder mixtures for granulation experiments. Then, each powder mixture was granulated under different twin-screw granulation process settings followed by oven-drying. Finally, granule size, granule strength and granule flow were determined for all the different produced granules. In the second part of the study, a TPLS model was developed to understand the effect of the raw material properties and process parameters on granule quality attributes. In the third part of the study, the TPLS model was used to predict an optimal formulation composition and twin-screw granulation process settings for a new API based on its determined critical material properties. In this case-study, suitable formulation compositions and corresponding optimal process settings for three different API contents were selected in order to obtain granules with desired quality attributes. This approach could be very beneficial during the formulation and process development of new APIs as the availability of the API is then limited. A stepwise overview of the approach to develop the TPLS model is shown in Figure 1.

# Materials

15 different APIs, 9 fillers and 3 binders (Table 1) that are intended for immediate release formulations were used in this study. The materials were purchased from Granules India (Hyderabad, India), BASF (Ludwigshafen, Germany), Siegfried PharmaChemikalien (Minden, Germany), Utag (Almere, The Netherlands), Polydrug Laboratories (Ambernath, India), FARMHISPANIA (Barcelona, Spain), Mallinckrodt (Dublin, Ireland), The Dow Chemical Company (Midland, US), Ashland (Covington, US), Meggle (Wasserburg, Germany), DFE Pharma (Veghel, The Netherlands), FMC BioPolymer (Cork, Ireland), Cargill (Minneapolis, US), Roquette (Lestrem, France) and Cargill (Minneapolis, US). An overview of the materials is shown in Table 1.

# Methods

# Raw material property database

The raw material property database consists of two parts. One part contains 39 physicochemical and solid state properties of the APIs and fillers, while the other part holds 9 properties of the 3 binders used in this study.

# APIs and fillers

# Laser diffraction

Laser diffraction (Mastersizer 2000, Malvern Instruments, Worcestershire, UK) was used via a dry dispersion method to measure a volume-based particle size distribution. Powder was fed towards a 550 RF lens at a rate of 3.0 G, using a standard jet pressure of 2.0 bar. Each powder was measured in triplicate and analysed by the Mastersizer 2000 software. The 10 %, 50 % and 90 % cumulative undersize fraction of the size distribution were reported by d10, d50 and d90, respectively.

# Bulk and tapped density

A known mass ([m] = g) of each powder was poured into a 250 mL graduated cylinder to record the bulk volume ([Vb] = ml). Consequently, the graduated cylinder was tapped 1250 times using a tapping machine (J. Engelsman, Ludwigshafen, Germany) to record the tapped volume ([Vt] = mL). Bulk ([] = g/mL) and tapped ([] = g/mL) density were calculated by Equation and 1 and 2 , respectively.

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# True density and porosity

An AccuPyc 1330 helium pycnometer (Micromeritics, Norcross, GA, USA) was used to measure true density ([ρtrue] = g/ml) of each powder. The equilibration rate was set at 0.0050 psig/min and 10 purges were performed for each test. Each powder was measured in duplicate. Powder bed porosity (ε, dimensionless) was calculated using Equation 3.

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# Ring shear test

Each powder was analysed in triplicate in a ring shear tester (RST-XS, Dietmar Schulze Schüttgutmesstechnik, Wolfenbüttel, Germany) to measure powder flowability and cohesivity. First, a pre-shear step was performed by applying a normal load of 1000 Pa on the sample. Next, three consolidation stresses of 400, 600 and 800 Pa were used to provide shear stress on the powder. Powder flowability is characterized as the ratio of the unconfined yield strength ([σc] = Pa) to the major principal stress ([σ1]= Pa), defined as the dimensionless flow function coefficient (ffc) (Equation 4). Powder flowability under influence of gravity was characterized by the bulk (ffp) (Equation 5) and consolidated (ffrho) density-weighted flow (Equation 6). In the latter equation, density under consolidation (1000 Pa) is represented by , whereas represents the density of water. Furthermore, powder cohesivity (τc) was described as the intercept of the yield locus with the shear stress axis. For further details on analysis and interpretation of ring shear test data, the reader is referred to Schulze et al. (Schulze, 2008).

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# Powder elasticity and plasticity

A fully instrumented compaction simulator (Styl’one evolution, Medelpharm, France) was used to determine the elasticity and plasticity of each raw material powder. Compacts were prepared using 10 mm flat faced Euro B-tooling (Natoli Engineering Company, Saint Charles, MO, USA) with approximately 15 kPa of pressure and 18 mm fill depth. A compaction speed of 10 mm/s was applied. Prior to manual powder filling, the die was manually lubricated with magnesium stearate. For each studied material, 5 compacts were prepared. After compaction, a force-displacement curve (Figure S1) was established by the ANALIS software. Work of compression (in J) was calculated as area ABC, elastic energy (in J) was calculated as area DBC and work of compaction as ABD. Elastic recovery ([Elas] = %) was calculated as per Equation 7. Specific work of compaction ([WoC] = J/g) was calculated using the recorded masses ([m] = g) of compacts produced (Equation 8).

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# Powder rheology

As powder flow depends on multiple physical properties such as particle size, cohesivity, shape, texture, particle stiffness and density, it is difficult to describe it by a single value. Therefore, a FT4 powder rheometer (Freeman Technology, Tewkesbury, UK) was used to measure several powder flow characteristics. Compressibility, aeration and variable flow rate tests were performed on the FT4 equipment. For each of the following test, the powder bed was first preconditioned. A preconditioning step is needed to start with a standardized packing of the powder particles. All powder rheology tests were performed in triplicate.

# *Stability and variable flow rate*

The resistance (i.e., required energy in mJ) of a powder is measured by a moving blade up and down through the powder bed. First, seven consecutive test cycles at 100 mm/s were executed to obtain a stable flow energy. Consequently, the flow energy value was measured while gradually reducing the blade tip speed (100, 70 , 40, 10 mm/s). The Basic Flow Energy ([BFE] = mJ) is the flow energy at 7th test, while the Flow Rate Index ([FRI] = dimensionless) is the ratio of the flow energy at 10 mm/s and 100 mm/s.

# *Compressibility*

The powder was compressed under increasing normal stress (0.5, 1, 2, 4, 6, 8, 10, 12 and 15 kPa) using a vented piston. Compressibility ([Com] = %) is defined as the relative change in volume at the end of the test.

# *Aeration*

An air flow was provided from the bottom of the vessel. The air velocity was gradually increased (0, 0.5, 1, 2, 4, 6, 8, 10, 15, 20, 30 and 40 mm/s) during the test. At each air velocity, the corresponding flow energy was measured. The flow energy (in mJ) at 40 mm/s was reported as AE40 ([AE40] = mJ). The ratio of the flow energy at 0 mm/s and at 40 mm/s was reported as AR40 ([AR40 ] = dimensionless).

# Charge density

Charge density was measured in triplicate using an electric charge analyser (GranuGharge, Granutools, Awans, Belgium). A vibrating feeder was used to feed 30 mL powder into two stainless steel tubes arranged in a V-shape to induce an electrostatic charge of the powder. Thereafter, the charged powder was collected in a Faraday cup connected to an electrometer. Charge density ([CD] = C/kg) was calculated as the ratio of net charge to the mass of the powder bed. The absolute value of the charge density was taken, as the net charge could be either negative or positive. All samples were measured in triplicate.

# Specific surface area

Before specific surface area ([SSA] = m²/g) measurements were executed, the samples were degassed in vacuum (VacPrep Micrometrics, Norcross, USA) for 24 h at 60 °C and purged with nitrogen for 1 h to remove impurities. Afterwards, the adsorption isotherm was determined by nitrogen adsorption (TriStar 3000 V6.08A, Micrometrics, Norcross, USA) and SSA was derived using the Brunauer-Emmett-Teller theory.

# Water binding capacity

Water binding capacity ([WBC] = %) is the tendency of a powder to bind and to hold water. 5.00 g of each material was transferred into centrifuge tubes and suspended in 20 mL of demineralized water. These tubes were centrifuged (Heraeus Multifuge 3 S-R, Thermo scientific, USA) at 4000 rpm for 25 minutes. The supernatant was discarded and the sample weight ([m] = g) was recorded. WBC was calculated as per Equation 9. Any negative values that results from the powder dissolving during the experiment were considered as zero.

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# Solubility

The maximal solubility ([Strue] = g/100mL) of each powder was empirically determined by gradually adding powder to 100 g of demineralized water. The temperature of the mixture was kept constant at 23 °C. A petri dish was used to protect the mixture from evaporation and a stirring bar was added to obtain optimal wetting of the powder. More water was added when the maximal solubility was exceeded or additional powder was added when maximal solubility was not yet reached. The maximal solubility was calculated by Equation 10.

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Where is the amount of powder, is the true density of the powder, is the initial amount of water, is the density of water at 23 °C and is the additional volume of water. As maize starch and the different grades of microcrystalline cellulose are insoluble, their solubility value was set at 1x10-8 g/100mL.

# Dissolution rate

A customized closed configuration system of the USP4 Flow-Through Dissolution Systems (Figure S2) (Sotax, Allschwil, Switzerland) was used to determine dissolution rate. The configuration consisted of 4 parts: (i) a piston pump (Sotax Cp 7-35, Sotax, Allschwil, Switzerland) to transport the dissolution medium through the system, (ii) a flow cell (Sotax CE 7 smart, Sotax, Allschwil, Switserland) containing a membrane (Float-A-Lyzer G2 Dialysis Device, Spectrum Laboratories, Rancho Dominguez CA, VS) of 1 mL. 200 mg sample was added to the membrane. (iii) A media reservoir filled with 250 mL demineralized water. (iv) An autosampler (Agilent 8000 Dissolution Sampling Station, Agilent Technologies, Santa Clara, U.S.) coupled to the media reservoir to collect 5 mL samples after 1, 3, 5, 10, 20, 30 and 60 min.

The collected samples were analysed by UV-VIS spectrophotometry (UV-1650 PC, Shimadzu, Suzhou New District, China). A calibration model was first established to determine the concentration for each powder, except for maize starch, microcrystalline cellulose, lactose and mannitol. Maize starch and microcrystalline cellulose were not measured due to their insolubility. As lactose and mannitol do not absorb UV, indirect measurements were needed for both materials. Lactose (Enzym Bio-analysis Lactose/D-glucose, R-biopharm AG, Darmstadt, Germany) and mannitol (D-mannitol assay kit, Megazyme, Wicklow, Ireland) concentrations were determined by an enzymatic detection kit. Both methods indirectly measured the sample concentration by detection of nicotinamide-adenine dinucleotide hydrogenate after enzymatic reactions. For all measured powders, the fraction powder dissolved after 1, 3, 5, 10, 20, 30 and 60 min were expressed as DR1, DR3, DR5, DR10, DR20, DR30 and DR60, respectively.

# Sorption properties

Hygroscopicity or water sorption behaviour of the studied materials was determined with dynamic vapour sorption (DVS) (DVS intrinsic, Surface Measurement Systems, London, U.K). First, approximately 15 mg powder sample was dried at 25 °C under a dry nitrogen stream. Then, the relative humidity (RH) was gradually increased from 0 to 80 % in steps of 20 % to calculate sorption values (percentage of moisture uptake). Finally, the RH was again gradually decreased in steps of 20 % to measure desorption (percentage of moisture reduction). Sorption and desorption values at 40, 60 and 80 % RH were noted as S40, S60, S80, D40, D60 and D80, respectively. At 40 and 60 % RH, sorption values were subtracted from desorption values to calculate hysteresis values (i.e., H40 and H60).

# Contact angle

Powder wettability was determined through contact angle measurements applying a drop shape analyzer (DSA30, Krüss, Hamburg, Germany). Before contact angle measurements, pure raw material was tabletted under high force using a single station tablet press (Korsch EKO, Korsch, Berlin, Germany). The tablet porosity did not exceed 10 % and draining of the liquid drop via interparticle and intraparticle pores was therefore limited. The sessile drop method was used for these measurements. A water drop of 5 µL was applied on a tablet and the contact angle was measured after 1 (CA1), 30 (CA30) and 60 (CA60) s. The contact angle ([CA] = °) was calculated from the Young-Laplace equation (Equation 11).

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Where (in Pa) is the pressure across the fluid interface, (in J/m²) is the surface tension and r1 and r2 (in m) are the radii of curvature.

# Binder-specific properties

Binder-specific properties were partly taken from a study of Vandevivere et al. (Vandevivere et al., 2020).

# Dissolution rate

Binders (10 % w/w) were added to demineralized water and mixed for 30, 60 or 90 s. Subsequently, the mixture was filtered using a cellulose-based filter (Grade 2, Whatman, USA). The fraction of dissolved binder was measured via the refractive index. For each binder, a calibration curve was established. Tests were performed in triplicate and the fraction binder dissolved after 30, 60 and 90 s was expressed as BDR30, BDR60 and BDR90, respectively.

# Surface tension

A Drop Shape Analyzer (DSA 30, KRÜSS, Hamburg, Germany) was used to determine the surface tension (ST) of an aqueous binder dispersion (8 % w/w) via the pendant drop method in air. For each binder, the curvature of a droplet was used to calculate the surface tension. Experiments were performed in triplicate.

# Viscosity

The dynamic viscosity of an aqueous binder dispersion (8 % w/w) was measured using a rotational rheometer (HAAKE MARS® III, Thermo Scientific, Massachusetts, USA) with the plate-plate technique. A gap size between 0.9 and 1.1 mm was applied, while temperature was set at 25 °C. 5 mL of the binder dispersion was transferred between the two plates. The viscosity values (mPa∙s) were derived from a total of 20 data points when the shear rate varied from 0.1 to 1000 s-1.

# Contact angle

Similar to 3.1.13, powder wettability was determined through contact angle measurements using a drop shape analyzer (DSA30, Krüss, Hamburg, Germany). Two set of experiments were performed. For the first set the contact angle of demineralized water on a pure binder tablet was determined (see 3.1.1.13). For the second part, the contact angle of an aqueous binder dispersion (8 % w/w) on a hydrophobic polytetrafluoroethylene surface was determined. Experiments were performed in triplicate. The contact angle calculation was calculated using aforementioned Equation 11. The hydrophilic contact angle for binders after 1, 30 and 60 seconds was reported as CAb1, CAb30, CAb60. The hydrophobic contact angle was reported as CAbh.

# Overview

An overview of the characterization techniques, the corresponding descriptor and the abbreviation of the descriptor are shown in Table 2.

# Blend ratios

Ten different formulations were selected for granulation experiments. The selection of APIs and fillers was based on PCA of the API material characterization data and filler material characterization data individually (see 4.2). Next, the complete dataset of API and filler material properties was subjected to PCA to link an API with a filler (see 4.2). For one formulation, a mixture of two fillers was used (Formulation 6). For each selected formulation the API content was 10, 40 or 70 %, resulting in a total of 30 different blends. Binders were added dry in a concentration of 2 or 5 %. Binders were added dry because the binder solubility in aqueous dispersions is limited and the pumpability and control of a constant liquid flow for highly concentrated binder dispersions is limited. The allocation of a binder to a API/filler combination was done at random. Table 3 gives an overview of the 30 different formulation blends.

# Process conditions

# Granulation experiments

All raw materials from each formulation blend were preblended in a tumbling mixer (Inversina Bioengineering, Wald, Switzerland) for 15 minutes at 25 rpm. Granulation experiments were performed using the granulation module of the ConsiGma™-25 unit (GEA Pharma Systems, Collette, Wommelgem, Belgium). This granulation module consists of two 25 mm diameter co-rotating screws with a length-to-diameter (L/D) ratio of 20:1. The preblend was gravimetrically fed to the granulation module by a K-tron KT20 loss-in-weight feeder (Coperion K-tron, Niederlenz, Switzerland). Granulation liquid (i.e., demineralized water) was added before the first kneading zone. Therefore, a twin-peristaltic pump was positioned out-off-phase and connected to silicon tubing with an internal and external diameter of 1.6 and 2.4 mm, 1.6 and 3.2 mm, 1.6 and 4.8 mm or 1.6 and 6.4 mm, respectively. The silicon tubes were connected to nozzles with an orifice of 0.8, 1.6, 2.4 or 3.2 mm. The selection of tubes and nozzles depended on the liquid flow rate. After wetting, the wetted mass is sheared and compressed in a first kneading zone, this zone consists of 6 kneading elements (L=D/4 for each kneading element) arranged at an angle of 60 degrees. After passing a small conveying zone (L=1.5D), granules were further processed in another kneading zone arranged identically to the first kneading zone. The granules were then transported by conveying elements (L=1.5D) towards the end of the granulator. At the end of the screws, two small kneading discs (L=D/6 for each kneading element) were positioned to limit the fraction of oversized granules. Before sample collection, a stabilisation period was needed to reach steady-state conditions. All collected granules were oven dried (24 h, 40 °C, 25 % RH) prior to further granule characterization.

# Design of Experiments

A 2-level full factorial Design of Experiments (DoE) was performed on each formulation blend to investigate the influence of the granulation process parameters MFR and L/S ratio on the granule quality attributes. Each DoE resulted in 4 experiments and 3 centerpoint experiments. MFR was varied from 10 to 20 kg/h, while the applicable L/S ratio ranges were experimentally determined for each formulation blend. L/S ranges were chosen so that both very small granules and oversized granules were obtained. Operating outside these L/S ranges would either result in ungranulated powder or in the formation of paste.

# Product quality attributes

# Granule size

An image analysis system (QICPIC particle size analyzer, Sympatec, Clausthal-Zellerfeld, Germany) was used to measure the granule size distribution based on the equivalent projected circle. Samples of 15 g were measured in triplicate. The fraction of ungranulated raw material was defined as fines, it corresponds to the size fraction smaller than 200 µm. Particles larger than 2000 µm were defined as oversized granules.

# Friability

Granule friability was measured to determine granule strength using a friabilator (Pharmatest PTF E, Hainburg, Germany). Before each measurement granules were pre-sieved at 250 µm. Consequently, 10 g (initial weight ([Iw] = g)) of the fraction larger than 250 µm was combined with 200 glass beads (diameter 5 mm) and subjected to 250 rotation in 10 min. Then, the fraction smaller than 250 µm was removed and the remaining mass (final weight ([Fw] = g)) was weighted. Friability was calculated using Equation 12. Experiments were performed in duplicate.

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# Granule flow

Granule flow was measured using the GranuHeap instrument (GranuTools, Awans, Belgium). After manually filling the initialization tube with 60 mL of granules, the tube was lifted at a constant speed of 5 mm/s. Hereafter, granules formed a heap on the support. The support rotated subsequently around its axis to take 17 pictures of the shape of the granule heap. The pictures were used to calculate the angle of repose ([AoR] =°) as an indication for granule flow. Excellent (25-30°), good (31-35°), fair (36-40°), passable (41-45°), poor (46-55°) and very poor flow (56-65°) can be defined based on the measured AoR.

# TPLS modeling

Figure 2 illustrates a schematic overview of the structure of the developed TPLS model in this study. Munoz et al. (2) already showed that the TPLS model involves 4 different matrices, whereby the applied process conditions (matrix Z), the raw material properties (matrix X) and ratios in which these raw materials are combined (matrix R) determine the quality attributes (matrix Y). The mathematics behind TPLS modelling are extensively described by Munoz et al. (2). Prediction of the granule quality (Y) for a given X, R and Z can be performed by TPLS. First, the predictive power was tested by performing a cross-validation for all experiments of F1B1. The predicted values were then compared to the experimental values to investigate the goodness of the predictions. The predictive ability of the TPLS model was also evaluated for a case study where a suitable formulation with suitable process setting was defined for a new API (at 3 content levels) based on its determined properties. The following steps were therefore performed for this new API. First, powder characterization was performed for the new API to determine all raw material properties. Then, these API properties were added to the database of API and filler material properties to perform a new PCA. The score plot of the PCA was then created to determine the closest neighbours (i.e., powders having similar properties) of the API. Subsequently, the weighted (depending of the distance between the neighbouring powders and the new API) scores of the neighbouring powders were assigned to the new API. This is needed to add the new API to the initially developed TPLS model. In a next step, constraints were set on the composition of the new formulation, the desired granule quality and the desired process settings. Next, the granule quality attributes of 25,000,000 different scenarios were predicted (i.e., computational iterations). The prediction of a scenario is defined as the prediction of the granule quality of a certain formulation while applying certain process parameters, and while keeping the constraints into account. After each prediction, the predicted quality is compared to the desired quality. Based on these predictions, suitable excipients and 3 appropriate blend ratios were selected to obtain granules with 3 different API contents. Additional predictions were then performed for the selected formulation to establish contour plot for each of response. Finally, verification experiments were performed to compare predicted values with the experimental outcome.

# Data analysis

SIMCA 16.0 software (Umetrics, MKS, Umea, Sweden) was used to construct PCA models. MODDE Pro 12.0 (Umetrics, Sartorius Stedim Biotech, Malmö, Sweden) was used to analyse each DoE. TPLS analysis was performed by a user-developed MATLAB (R2016b, MathWorks, Natick, MA, USA) 220 toolbox (Phi\_1.8).

# Results and discussion

# Raw material database (X)

Binders behave differently once in contact with the granulation liquid and their relevant physical properties are different compared to those from the APIs and fillers. As suggested by Munoz et al. (Garcia-Munoz, 2014), the raw material database (X-matrix) consisted therefore of a sub-data matrix containing 39 raw material properties of 23 APIs and fillers and a sub-data matrix containing 9 binder-specific properties (Figure 2).

For the complete dataset only 15 of the 987 descriptors were missing (i.e., 1.51%). These missing data were due to failure of a few characterization techniques for certain materials. For example, contact angle descriptors were missing for theophylline micronized and metformin fine. For these APIs, it was not possible to make tablets with a porosity lower than 10 %, due to their poor compaction properties. This very low fraction of missing data does not further impact multivariate data analysis according to Nelson et al. (Nelson et al., 1996).

Before multivariate data analysis (PCA) and TPLS modelling were performed, data was pre-processed. First, unit variance scaling and mean-centering were performed. Unit variance was performed by dividing each value by the standard deviation of that descriptor, whereas the mean was subtracted from the data of each variable to mean-center. Therefore, the different numerical ranges of the descriptors were normalized and a repositioning of the coordinate system was obtained which improved the interpretability of the model. In addition, the numerical overweight of some descriptors was overcome by excluding descriptors representing similar raw material properties. The exclusion of similar descriptors was based on their goodness of prediction (Q2X). The Q2X of a variable is the cumulative predicted fraction of the variation of X using cross-validation. Hence, an unbalanced model was avoided and all remaining descriptors were equally important. Thus, the 39 API- and filler-descriptors were reduced to 19 descriptors (d50, , , , ε, ffc, τc, S40, Strue, DR60, CA1, WBC, Com, SSA, CD, Elas, WoC, BFE and AR40) and the 9 binder-specific descriptors were reduced to 5 (DR90, ST, CAb1, CAbh and Vis). These descriptors are shown in bold in Table 2. For each PCA, the goodness of fit of the model (R2X) and goodness of prediction (Q2X) was calculated. R2X relates to the amount of variability that is captured by the model. A two-principal component model was developed for each (sub)dataset, as this facilitates the interpretation and was sufficient to differentiate the powders according to their properties.

# Blend selection

PCA was applied on the refined (only including 19 descriptors) API and filler subset of the database as a helpful tool to differentiate between the 14 APIs and 9 fillers based on their raw material properties. The resulting loadings and score plots are shown in Figure S3 and S4, respectively. In both PCA plots, one principal component described the variance in density and flow related descriptors (, d50, ffc, com and ε), whereas the other principal component was related to solubility, water binding capacity and dissolution rate. For a more in depth interpretation of the loadings and score plots, the reader is referred to (Van Snick et al., 2018; Willecke et al., 2017). For both the filler and API subset, powders were selected with the aim to cover a broad range in raw material properties. Therefore, powders located at the borders of the scores plot were selected. In addition, less extreme powders that are located closer to the origin were also selected because these powders differ from powders located at the borders.

As a next step a PCA was also performed on the complete data set containing all 9 fillers and 14 APIs and all their properties to link an API with a filler. The scores plot (Figure 3 – top) clearly shows clusters of APIs (blue) and fillers (green) indicating fillers and APIs with similar raw material properties. Fillers are mostly located in the upper right quadrant of the scores plot indicating good flow properties as suggested by the loadings plot (Figure 3 – bottom). APIs from different quadrants in the scores plot were linked to fillers located in the same or in different quadrants in order to increase the variability in formulation composition because each quadrant is correlated to different raw material properties. For example, APIs from the upper left quadrant of the scores plot were combined with fillers from the upper right quadrant (Cel – SD100, Mpt\_µ – PH101) and fillers from the upper left quadrant (Nap – PH105). The differences in directions and distance of the arrow between API and filler from one quadrant to another quadrant even further increase variability. For example, the arrow between Cel and SD100 is from the left-to-right and, in addition, longer than the arrow between MPT\_µ and PH101 which is rather from bottom-to-top. Consequently, the formulation properties of Cel-SD100 and MPT\_µ-PH101 are very different. This approach results in a large variability in formulation composition. Ultimately, this was even further increased by varying the API content at 3 levels (10, 40 and 70 %) for each selected formulation (Table 2).

# Granulation experiments and granule quality attributes

The study resulted in a total of 210 experiments (10 formulations x 3 API levels x 7 DoE experiments) whereof 13 experiments could not be accomplished. This was observed for the blends consisting of 70 % of a low dense API: naproxen of F5B3 ( = 0.25 g/mL, = 0.35 g/mL) and celecoxib of F10 ( = 0.16 g/mL, = 0.27 g/mL). It was possible to gravimetrically feed these blends at 20 kg/h, but their volume exceeded the free volume in the granulator.

The L/S ratio ranges for each formulation and each blend were varied to obtain differences in granule quality. Since the variability in blend composition is very large, different L/S ratio ranges were required. An overview of the applied process settings per experiment is shown in TableS1. For example, a L/S ratio of 84 % was used to produce coarser granules for F5B1 (i.e., 10% nap – 85% PH101 – 5% HPMC), as this formulation lacks a soluble API or filler, hence requiring a high quantity of granulation liquid.

# TPLS modelling

# TPLS model development and interpretation

A two-latent variable (LV) TPLS model was fit to the data as R² only slightly increased when a third LV was added. Moreover, the addition of a third LV complicated the physical interpretation of the results. The Variable Importance for the Projection (VIP) plot was developed to highlight the most influencing raw material properties in the TPLS model (Figure 4). Generally, the variability in raw material properties with the highest importance explains the variability in granule quality attributes the most. DR60, Com, WoC, S40, WBC, , Strue were the seven most influencing raw material properties upon granule quality attributes. Flow-related properties (ffc, BFE, AR40), SSA and CD appeared to be less influential for the granule quality attributes. In addition, binder-specific properties were less important. This can be explained by the variability within a binder-specific property. This variability is generally lower because the binders are less different, as all three binders are all typically used for immediate release. In addition, as the binder content was only varied from 2 to 5 %, it is possible that these powders were less dominant than API/filler properties.

The effect of the raw material properties upon the different granule quality attributes was studied in more detail by interpreting their loadings for each LV. The first LV mainly captured the variability in AoR and fines fraction (Figure 5 – top). Fines fraction was correlated to the AoR, fewer ungranulated material (i.e, lower fines fraction) resulted in a better flow (lower AoR values). Furthermore, a higher DR60, Strue, BFE and tended to result in a better flow, while a higher ε, SSA, CD, WBC, WoC and S40 tended towards poorer flow. For the wet powder properties (i.e., Strue, DR60, WBC), a higher Strue and DR60 resulted in more or faster powder dissolution, respectively, consequently resulting in more granulated material and a smaller fines fraction as more liquid bridges are made. As less liquid is available for the granulation process, a higher WBC resulted in more ungranulated material.

For the dry powder properties (i.e., BFE, , ε, SSA and CD), it is suggested that their effect on AoR can be explained by the flow properties of the ungranulated powder. On the one hand, porous (ε) and electrically charged (CD) properties impair powder flowability, resulting in a higher granule AoR. On the other hand, a higher bulk density and BFE value typically corresponds to denser and larger powder particles with a better flow, thereby resulting in a negative correlation with AoR. It is not possible to give a good physical interpretation for each raw material property even though it has a high loading value. For example, it was observed that WoC and S40 negatively affected granule flow, but an explanation related to the granulation process cannot be given. The effect of WoC and S40 on the granule quality attributes was probably due to a mathematical coincidence, as WoC and S40 were clustered with WBC on the scores plot for APIs and filler (Figure 3 – top). This is due to the properties of MCC, as all MCC grades had high values for these descriptors.

The second LV captured the variability in granule size and friability (Figure 6 – top). Larger granules were typically stronger. A higher DR60 and Com tended to result in larger and stronger granules, while higher WBC, S40, WoC, and were linked to more fines and weaker granules. The previously mentioned mechanism (i.e., the creation of more liquid bridges) is also valid for the effect of DR60 and WBC on granule size and friability. Again, the effect of WoC and S40 was explained by their mathematical coincidence. A lower powder bed density, lower particle density and higher compressibility tended to result in larger and stronger granules. This suggested that a higher available void volume (i.e., inter- and intra-particulate voids) of the powder bed in the granulator is beneficial for the granulation process. It is possible that the wetting and (re)distribution of liquid is enhanced for those powders. First, the penetration of the liquid into the inner core of the powder bed could be enhanced and secondly the redistribution of the liquid in the kneading zones could occur more easily because the powder volume can be reduced. This is in contrast to a denser powder bed where the liquid penetration or liquid distribution is more hampered due to the more efficient packing of the denser particles.

The effect of the process parameters upon the different granule quality attributes was also studied by interpreting their loadings for each LV. From these figures (Figure 5 – bottom and Figure 6 – bottom), it is clear that granules with a smaller fines fraction, a larger oversized fraction, a lower friability and a lower AoR were obtained when a higher MFR and L/S ratio were applied. For both LVs, a higher loading was observed for L/S ratio, indicating its dominant influence on granule quality attributes. This result was expected as this has already been reported by multiple studies (5–11). Overall, the raw material properties were more influencing the granule quality attributes than the process settings because the loadings for most raw material properties were higher for both LVs (Y-axes on Figure 5 and 6 (middle and bottom)).

# Predictions using developed TPLS model

Using the developed TPLS model, it is possible to predict granule quality attributes (Y) for a given X, R and Z. In this section, the predictive performance is first evaluated by cross-validation of one of the blends. As a final model verification exercise, a suitable formulation and corresponding process settings were predicted for a new API which was not used for the model development.

# Cross-validation

The predictive quality of the developed TPLS model was first evaluated for the F1B1 formulation. The 5 experiments covering the completely performed DoE of F1B1 (10 % ibu, 85 % 200M and 5 % E5) were tested for this leave-one-out cross-validation exercise. The predicted granule quality attributes based on the material properties and process settings (used as input in the model for granule quality attribute prediction) were compared to the experimental values for friability, AoR and fines fraction and oversized granules (Figure 7). Predicted values were (very) different from the experimental values for experiments at low MFR – low L/S, low MFR – high L/S and high MFR – low L/S. Good predictions were seen at intermediate process settings and at high MFR – high L/S. At these process setting, the predicted values were very close to the experimental values demonstrating some predictive quality of TPLS model, however not over the entire design space.

# TPLS Model use for formulation development

The ability to predict granule quality for given combination of X, R and Z could be helpful in formulation development. In this section, API X was considered as a new API. After performing a full raw material characterization for this API X, appropriate excipients and processable ranges were predicted using the TPLS model to result in granules with the desired quality attributes. A stepwise overview to obtain suggestions for the selection of a formulation and the process settings resulting in the desired granule quality for new APIs is schematically shown in Figure 8 and intensively discussed in following sections.

# Advanced surrogate method

As API X was not used in the granulation experiments, the scores of API X could not be determined by the TPLS model. Hence, its location in the regressor space cannot be found. To overcome this issue, an advanced surrogate method was used. First, PCA was used to create a score plot including API X, the 9 APIs and the 7 excipients that were used during the granulation experiments (Figure 9). Subsequently, the closest neighbours of API X were determined according to a k-nearest neighbours algorithm (Triguero et al., 2017). Including too many materials may result in uninvestigated interactions, including too few materials may result in properties not being captured well. Hence, the weights of following 5 powders were used to describe the properties of API X: 59.3 % ‘Ibu’, 20.4 % ‘Nap’, 8.7% ‘T\_A\_200’, 7.5% ‘P\_SF’ and 4.1% ‘Cel’. These weights are the inverse distance of API X to its neighbours.

# Setting constraints

*Desired formulation*

As multiple formulations can lead to the desired granule quality, constraints were given to define the formulation by TPLS. The content of API X was allowed to vary between 2 and 25 % (w/w), so that three formulations with a different API content (i.e., 3, 12 and 24 %) could ultimately be selected using the same excipients. The new formulation also had to include MCC due to its added value for granulation robustness (Portier et al., 2020a). The content of the most suitable grade of MCC (i.e., filler 1) should be between 10 and 20 % (w/w). A binder was needed in a fraction between 2 and 5 % (w/w), as the model was trained for this range of binder content. Finally, one soluble filler (i.e., filler 2) was required to complete the formulation to minimize the amount of granulation liquid.

*Desired granule quality*

As TSG is an intermediate process step, a specific granule quality is demanded for further downstream processing. In this study, the fines fraction was limited to 10 % to avoid filter clogging in the drying cells during the drying process. Friability could not exceed 20 % to yield granules which resist the impact of the wet and dry transfer line and the drying phase. In addition, the angle of repose had to be below 45° to guarantee a passable flow. No constraints were set on the oversized fraction because a small fraction in oversized granules is typically correlated with a larger fraction in fines (see constraint on fines) and an excess in oversized granules can be milled in the conditioning unit of the ConsiGma™-25 system. It has to be emphasized that the desired granule quality is chosen based on the experience of the authors. However, the desired granule responses can be easily modified before the start of the predictions.

*Process settings*

Constraints were also set on the process settings. MFR was only allowed to vary between 10 and 20 kg/h, as those ranges were also used to calibrate the TPLS model. L/S could not exceed 20 % to avoid a too long drying time. Similar to the constraints on the desire granule quality, the maximal allowed L/S ratio can also be modified.

# Selection of optimal excipients and process settings

In this section, different scenarios were predicted. The prediction of a scenario is defined as the prediction of the granule quality attributes for a certain formulation, whereof the formulation properties are dependent of the properties of the selected raw materials (X) and the ratios in which these raw materials are combined (R), processed at specific process parameters (Z), herewith taking all of the aforementioned constraints (section 4.4.3.2) into account. The different scenarios could differ in filler 1 (PH101 or PH105), filler 2 (200M, 11SD, 160C, T80 or 100SD), binder (E5, K30 or KEF), API content and excipient content (resulting in different blend ratios) and in process settings. Clearly, an infinite number of combinations are possible. As a consequence, an infinite amount of scenarios could be predicted. Therefore, a total of 25,000,000 different scenarios were predicted. Subsequently, after each prediction, the predicted granule quality was compared to the desired quality set at constraints.

Table 4 shows the fraction in successful predictions for each excipient. This is the fraction of predictions (only predictions at which the certain excipient was involved), that resulted in the desired granule quality. As the fraction of successful predictions was slightly higher with PH101, it was chosen as filler 1. Although Lactose 200M did not have the highest fraction of successful predictions, it was selected as filler 2 in the formulation. The higher dissolution rate of 11SD and 160C explained the higher fraction of successful predictions as a higher dissolution rate was related to a lower fraction of fines, a lower friability and a lower AoR (Figure 5 and 6). However, the higher dissolution rate also reduces the process robustness, since small deviations in liquid flow rate or mass feed rate during manufacturing could strongly affect the granule quality. Therefore, the selection of 200M was justified. HPMC E5 and PVP K30 clearly had a higher probability to result in the desired granule quality compared to HPC KEF. HPMC E5 was selected as it resulted in the highest success rate.

In a next step, only the successful predictions with the formulation consisting of API X, lactose 200M, MCC PH101 and HPMC E5 were taken into account to create Figure 10. This figure plots the fraction of successful predictions for each content of each raw material which results in a granule quality within specifications. This allowed to identify the content of a certain raw material in the formulation that has a higher probability to result in granule quality within the set specifications. Multiple combinations of raw materials could result in the desired granule quality. In general, a lower binder content resulted in more successful predictions, as the highest peak was observed around 2 % (Figure 10 – yellow peak). This result is in contrast to the findings of Keleb et al. and Dhenge et al. (Dhenge et al., 2012b; Keleb et al., 2004). Granule growth was favoured in these studies at higher binder concentration. However, a wet binder addition was used in these studies in contrast to our study. In our study a higher content of filler 2 (i.e., lactose 200M) at the expense of the binder resulted in more granule growth. As the residence time in a twin-screw granulation process is rather short (i.e., 4-20 seconds (Vercruysse et al., 2012)), it is suggested that the high dissolution rate of the hydrophilic filler is more effective for granule growth due to the formation of strong liquid bonds than a larger fraction of dry binder that still needs to be activated during the short residence time in the granulator. Further, lower MCC concentrations also yielded the desired granule quality more often (Figure 10 – red peak). According to the constraints (see 4.4.3.2), the L/S ratio was not allowed to exceed 20 % but higher L/S ratios are generally needed at higher MCC content due to their high WBC (Portier et al., 2020a), explaining the lower probability to result in successful predictions. Less successful predictions were also observed when the API content increased, this is probably due to its hydrophobic characteristics (Figure 9). More successful predictions were observed using a higher 200M content as this hydrophilic filler is advantageous for granule growth. The decrease observed at a 200M content above 78 % was due to the lower number of predictions executed at a high lactose content, as in that scenario the binder, API and MCC content all had to be lower in order not to exceed the total of 100 %.

In this case study, the API content was varied at three levels, yielding granules with a different potency. The blend composition for these 3 API concentrations which are predicted to provide the desired granule quality attributes are shown in Table 5. In a next step, additional predictions, during which the process settings for each of these 3 formulations were varied, were performed. This allowed to establish contour plots for friability, fines and AoR for each blend (Figure 11). Only the area (i.e., combination of MFR and L/S ratios) which yielded the desired granule quality, according to the prediction by the TPLS model, was coloured in the plots. The colour gradient in Figure 11 corresponds to the predicted change in fines, friability or AoR at different combinations of MFR and L/S ratio. It can be seen that the area of successful predictions was very similar for all three formulations. Although formulation 3 contained more hydrophobic API at the expense of the hydrophilic filler lactose, a similar granule quality was predicted for the combination of MRF and L/S values. This can be explained by other properties of API X, having a favourable effect on granule growth. In contrast to 200M, API X has a lower density and a higher compressibility which have previously been identified having a positive effect on granule growth. It is suggested that a better liquid distribution could be obtained for formulation 3.

Finally, the predicted granule quality attributes for each of the three blends were compared to the experimentally determined granule quality attributes. The four edges of the contour plot (Figure 11) and a centerpoint were verified. The comparison of the experimentally determined granule quality attributes with the predicted granule quality was shown for the blend containing 12 % API in Figure 12. A similar comparison was also seen for the blends with 2 and 24 % API. Similar to the cross-validation results (Figure 7), the best predictions were observed for the intermediate and high MFR – high L/S process settings. At these process settings the predicted values were, except for the oversized fraction, close to the experimental values, indicating some predictive quality of the TPLS model. It is possible that the fraction of oversized granules is harder to predict as it is a cut-off value (i.e., >2000 µm) of the granule size distribution to indicate the granule size. The validation experiments showed that large oversized fraction and a fines fraction of almost zero was observed at high L/S and high MFR, indicating that a paste would be formed at higher L/S ratio. However, an actual cut-off for the formation of a paste cannot be predicted by the model. Possible reasons of the TPLS model prediction challenges are discussed in the next section.

# Limitations, challenges and future perspectives

In general, the predictions of current TPLS model are only valid for the studied experimental space and for fixed conditions such as the screw configuration and screw speed because both have an impact on the granule quality (Portier et al., 2020c; Thompson and Sun, 2010; Vercruysse et al., 2015). Further, only dry binders were added to the powder mixture.

The predictions, either for the cross-validation (Figure 7) and the new formulation (Figure 12), were not reliable for all process setting (lower MFR and lower L/S ratio). As TPLS is a linear regression technique, it allows a straightforward interpretation which gives an enhanced process understanding. However, this method has a lower predictive ability compared to non-linear techniques (Bylesjö et al., 2006).

Multiple studies have already shown interactions (i.e., non-linear correlations) between different process settings (MFR, screw speed and/or L/S ratio) (6,22–26). Most likely interactions between the process settings or between raw material properties and process settings occurred, resulting in a non-linear correlation with the granule quality. In addition, extreme formulations (e.g., formulation 5 which lacked soluble components and which was processed with L/S ratios up to 84 %) were selected for the granulation experiments. This is beneficial for process understanding as the inclusion of more divergent formulations allows to highlight the most influencing raw material properties. In addition, a more divergent dataset also increases the probability that a future API will fall within the already investigated ranges (i.e., the regressor space). However, the very divergent formulations processed with different process settings resulted in diverse granule quality attributes. This enlarges the regressor space, making it more complicated to find the correct real values in that space. In general, the addition of granulation experiments, performed with new APIs or excipients, will also increase the predictive ability of the TPLS model because it is a data-driven model. The large database can also be used for other predictions such as non-linear PLS. As these techniques make non-linear correlations, their predictions may be closer to the real values.

# conclusions

In this study, a TPLS model was developed to link raw material properties, the ratios in which these raw materials were combined and the applied process parameters for a twin-screw wet granulation process. Very divergent APIs and excipients were combined for granulation experiments under different process settings. This allowed to enhance the process understanding of the granulation process. First, the effect of the different raw material properties on granule quality was studied. The variability in dissolution rate, compressibility, water binding capacity, powder density and solubility affected the variability in granule quality the most. Overall, the raw material properties were more influencing the granule quality attributes than the process parameters. Further, the predictive ability of the TPLS model was used to select a suitable formulation for a new API. A first run of predictions suggested to use lactose 200M, microcrystalline cellulose PH101 and HPMC E5 as suitable excipients in combination with different API contents. However, the comparison of the experimental granule quality with the predicted granule quality at different process settings indicated that the predictive ability of TPLS was only valid at specific process settings. However, despite the current pitfalls, the TPLS model has the potential to predict a reasonable starting point for formulation and process parameters for new APIs. This approach can reduce the experimental effort, the consumption of the expensive API and the development time to select a suitable formulation and to find optimal process parameters during product development. In a next step, other modelling techniques such as non-linear PLS can be used to increase the predictive power.

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