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A novel approach to support formulation design on twin screw wet granulation technology: Understanding the impact of overarching excipient properties on drug product quality attributes

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List of abbreviations:
  API - Active pharmaceutical ingredient
  BET - Brunauer, Emmett, Teller
  DoE - Design of Experiments
  ffc - Flow function coefficient
  HPMC - Hydroxypropyl methylcellulose
  IPC - in-process control
  L/S - Liquid-to-solid
  LOD - Loss on drying
  MCC - Microcrystalline cellulose
  MLR - Multiple linear regression
  P/O - predicted to observed
  PC - Principal component
  pCQAs – Potential critical quality attributes

PCA - Principal component analysis
PSD - Particle size distribution
PVP - Polyvinylpyrrolidone
QbD -Quality by Design
rpm - rounds per minute

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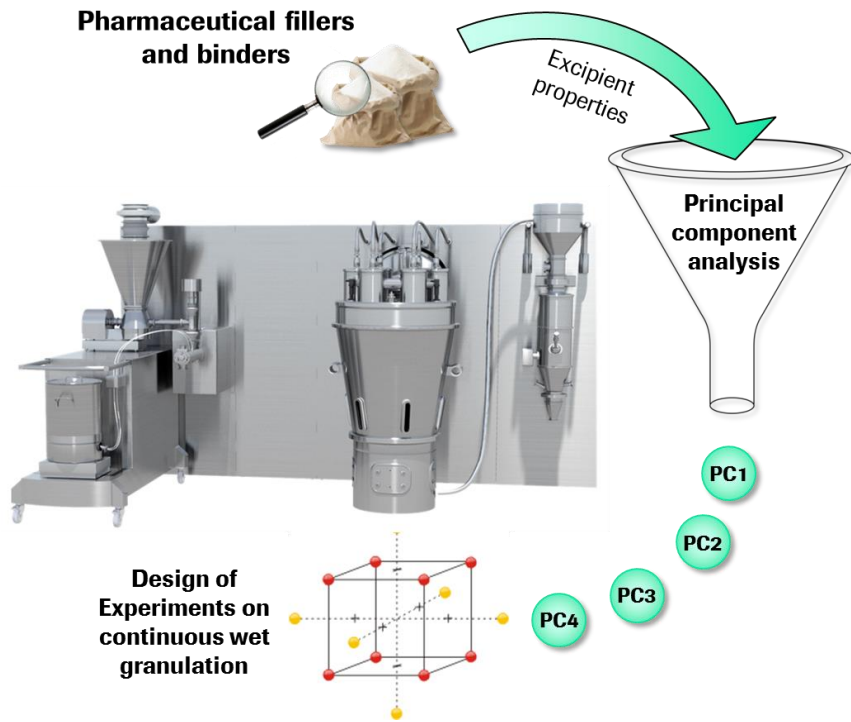
Letter to the editor

Dear Prof. Siepmann,

Please find attached our manuscript entitled *"A novel approach to support formulation design on twin screw wet granulation technology: Understanding the impact of overarching excipient properties on drug product quality attributes"* to be considered for publication as a research article in *International Journal of Pharmaceutics*.

The submitted work is the follow-up study to the paper which was recently published by your journal ("Identifying overarching excipient properties towards an in-depth understanding of process and product performance for continuous twin screw wet granulation"). This study presents a combination of principal component analysis with design of experiments with the objective to understand the impact of excipient characteristics on granule and tablet properties produced via continuous twin screw wet granulation. The formulation understanding as well as the statistical models can be used to support a lean formulation development: to avoid unnecessary experiments, excipients with appropriate characteristics can be selected in order to compensate for unfavourable API properties. The predictive power of the model can be used for formulation optimization and troubleshooting, by selecting fillers and binders with appropriate properties to improve suboptimal granule or tablet characteristics.

A thorough understanding of the influence of the formulation composition and excipient characteristics on both process performance and the drug product's critical quality attributes is a fundamental part in the product design. Thus, we consider this study to be of high relevance, especially for continuous manufacturing processes.

This manuscript is not under consideration at any other journal and has not been rejected in the past by any journal. The document has not been published elsewhere in the same form in English or any other language.

We appreciate your support for the publication of this article in International Journal of Pharmaceutics.

On behalf of all authors,

Nina Willecke

Abstract

The overall objective of this work is to understand how excipient characteristics influence the drug product quality attributes and process performance of a continuous twin screw wet granulation process. The knowledge gained in this study is intended to be used for Quality by Design (QbD)-based formulation design and formulation optimization. Three principal components which represent the overarching properties of 8 selected pharmaceutical fillers were used as factors, whereas factors 4 and 5 represented binder type and binder concentration in a design of experiments (DoE). The majority of process parameters were kept constant to minimize their influence on the granule and drug product quality. 27 DoE batches consisting of binary filler/binder mixtures were processed via continuous twin screw wet granulation followed by tablet compression. Multiple linear regression models were built providing understanding of the impact of filler and binder properties on granule and tablet quality attributes (i.e. 16 DoE responses). The impact of fillers on the granule and tablet responses was more dominant compared to the impact of binder type and concentration. The filler properties had a relevant effect on granule characteristics, such as particle size, friability and specific surface area. Binder type and concentration revealed a relevant influence on granule flowability and friability as well as on the compactability (required compression force during tableting to obtain target hardness). In order to evaluate the DoE models' validity, a verification of the DoE models was performed with new formulations (i.e. a new combination of filler, binder type and binder concentration) which were initially not included in the dataset used to build the DoE models. The combined PCA (principle component analysis)/DoE approach allowed to link the excipient properties with the drug product quality attributes.

1. Introduction

Continuous twin screw wet granulation is a promising alternative to batch wet granulation technologies for solid dosage form manufacturing in the pharmaceutical industries due to its potential for an accelerated development process with a lean scale up and savings in drug substance [1]. Considering the difference in granulation process, and in particular the shorter granulation time of a continuous wet granulation process, compared to high shear wet granulation, the effect of excipients on process performance and product quality attributes may not necessarily be transferable. This understanding however is of fundamental importance as basis for a quality by design (QbD)-based formulation development [2]. A number of studies have been published which investigated different formulations processed via twin screw wet granulation in order to study the influence of excipient material attributes (e.g. particle size or water binding capacity) on the drug product's potential critical quality attributes (pCQAs) (e.g. granules particle size distribution and tablet tensile strength). Mainly, excipients like lactose [3],[4], microcrystalline cellulose [5], dicalcium phosphate, or mixtures thereof were used. Some formulations also contained active pharmaceutical ingredients (API), focusing on variation in API particle size [5], API hydrophobicity [6] or drug load [7]. For a tabular overview the reader is referred to the review of M. Tezyk [8]. By including hydroxypropyl methylcellulose as hydrophilic matrix former in formulations,

Vanhoorne et al. and Thomson and O`Donnel showed that controlled release formulations with sustained release over 16-20 hours were also processable via continuous twin screw wet granulation [9], [10]. However, it remains challenging to compare excipients with very different characteristics in the same study since the resulting formulations require e.g. different liquid-to-solid (L/S) ratios in order to obtain granules of good quality [11]. Therefore the above-mentioned studies focused on a limited variation in formulation composition, hence the obtained scientific conclusions can mainly be considered formulation specific.

For this reason, an important driver for this research work was to include excipients (fillers and binders) with different material properties in one experimental design and to systematically study their impact on process and product performance of a continuous twin screw wet granulation process. DoE is generally limited in the number of factors which can be studied due to limitations in the number of experiments that can be performed. Therefore, one of the main challenges was to investigate a broad range of excipient properties which might potentially impact the drug product's pCQAs as factors in the same DoE study. As previously described by the authors in [12], principle component analysis (PCA) was used to reduce large data sets of excipient characteristics (1 data set for fillers and 1 data set for binders) to a limited number of overarching properties (i.e. the principal components). These overarching properties explained most of the variability of the original excipient property data sets: 4 principal components (PCs) explained 98.4% of the overall variability in the filler data set, while 93.4% of the overall variability in the data set of binders was covered via 3 PCs. Moreover, PCA of the filler and binder data set allowed revealing similarities and differences in filler and binder characteristics among materials of different chemical nature as well as between material grades. PCA also enabled to identify those properties which were mainly responsible for these differences and similarities of the excipients. PCA and DoE were combined with the intention to understand the influence of excipient (filler and binder) characteristics and formulation composition upon granule and tablet attributes after continuous twin screw wet granulation. The objective was to develop statistical models which are capable of predicting the pCQAs after granulation and tableting for a certain combination of filler and binder as well as to select an optimal combination of filler and binder leading to desired drug product characteristics based on the models predictions.

Figure 1 depicts the step-wise systematic approach that was followed in this study [13]. The performance and results of steps 1-4 were published in [12], while steps 5-8 are presented in this publication. First, pharmaceutical fillers and binders suitable for twin screw wet granulation were selected and extensively characterized with regard to their physico-chemical properties and solid state characteristics (steps 1 & 2). PCA was then performed on the resulting data sets of excipient properties (1 PCA on filler data set and 1 PCA on binder data set) in order to identify the overarching properties, i.e. PCs (steps 3 & 4). Using these overarching properties as DoE factors, suitable combinations of fillers and binders can be selected based on an experimental design (step 5). In this study two commonly used low viscosity grade binders were selected. The resulting statistical DoE models were used to understand and predict the impact of the overarching excipient properties on granule and tablet quality attributes. In addition, the process performance of the selected formulations was evaluated (steps 6-8).
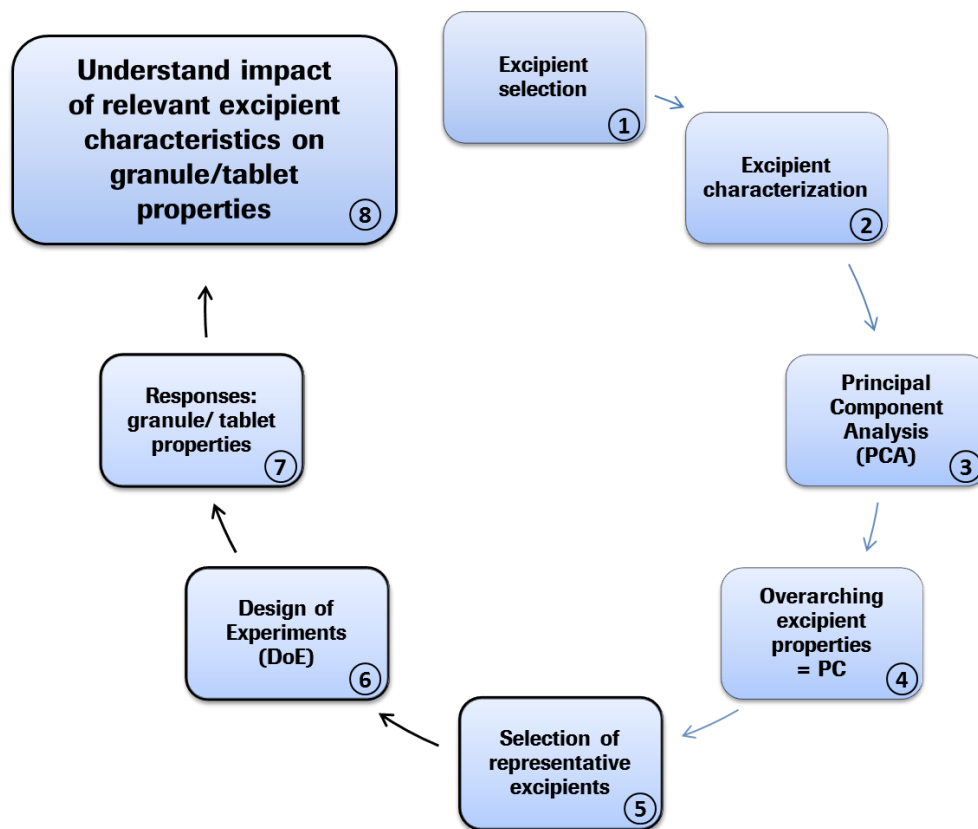
Figure 1. Stepwise overview of the systematic approach to generate formulation understanding

2. Material and Methods

2.1. Materials

Microcrystalline cellulose (Avicel PH101, Avicel PH105, Avicel PH301, FMC Biopolymer, Philadelphia, USA), α-lactose monohydrate (Pharmatose 200M, Pharmatose 350M, DFE Pharma, Goch, Germany and GranuLac 200, Meggle Group, Wasserburg, Germany) and mannitol (Parteck M200, Parteck Delta M, Merck, Darmstadt, Germany) were used as fillers. Hydroxypropyl methylcellulose (Pharmacoat 603, Shin Etsu, Tokyo, Japan) and polyvinylpyrrolidone (Kollidon K30, BASF, Ludwigshafen, Germany) were used as binders in this study. Croscarmellose sodium (Disolcel GF, Mingtai Chemical Co, Taoyuan Hsien, Taiwan), magnesium stearate (Mallinckrodt, St. Louis, USA) and colloidal silicon dioxide (Aerosil 200, Evonik, Rheinfelden, Germany) were used to prepare the final blend for tablet compression.

2.2. Experimental design

2.2.1. Identification of filler and binder types

The intention in this study was to investigate formulations which consisted of one filler and one binder. The selection of fillers included commonly used types suitable for wet granulation with differences in chemical nature (e.g. lactose, MCC, mannitol) and properties, such as water solubility or compression behavior (brittle/plastic). Further variability in excipient characteristics was obtained by selecting filler grades differing in particle size (e.g. Pharmatose 200M vs. Pharmatose 350M) and density (e.g. Avicel PH101 vs. Avicel PH301). The 8 selected fillers were extensively characterized as described in a previous paper [12]. Using PCA, the overarching properties of the filler data set were identified.

Kollidon K30 (PVP) and Pharmacoat 603 (HPMC) were selected as commonly used and low viscosity binder grades for wet granulation.

2.2.2. Selection of binder concentration

The binder concentration range for the DoE was defined at 1-2% (in the dry granules) based on the outcome of preliminary trials (data not presented). Due to the short granulation time, the binders were added as aqueous dispersions. The pre-trials revealed that the maximum binder concentration which could be added in the granule formulation was limited. First, the binder solubility in the aqueous dispersions is limited. Secondly, there is a limitation in pumpability and control of constant liquid flow for highly concentrated, highly viscous binder dispersions depending on the applied set-up of tubing and pumps (see section 2.3.1). Due to the limited water uptake capacity of pure lactose, this formulation was considered as the worst case for wet granulation, as it requires a low water content for granulation. For this lactose formulation, a binder concentration in the formulation of maximum 2% could be reached for both binder types. Although 2% binder concentration is well below the maximal concentration for HPMC and PVP recommended by the suppliers (i.e. 2-5%), the pre-trials showed that a binder concentration range of 1-2% resulted in pronounced differences in granule properties (e.g. granule PSD and granule friability). Hence, the selected concentration range was considered sufficiently discriminating. Furthermore, with a concentration range of 1-2% a controlled and reproducible pumpability was ensured.

2.2.3. Factors of the DoE

5 factors were studied in the experimental design. 3 factors were the score values of the 3 principal components (PC) derived from the PCA of the fillers data set which consisted of the fillers' physico-chemical and solid state properties [12]. These 3 PCs together defined the filler type in the formulation where PC1 represented the moisture-related, PC2 the flow-related and PC3 the density/particle size-related filler properties. In that way, three overarching filler properties were investigated in the DoE, while all underlying filler characteristics were indirectly included in the experimental design.The fourth qualitative factor defined the binder type (PVP or HPMC). The fifth factor represented the binder concentration in the dry granules varying between 1 and 2%. The binder types were not represented by their PCA score values in the experimental design and thus not selected by their overarching properties as this approach leads to the selection of high viscosity grade binders which had limitations regarding pumpability during processing (data not presented).

2.2.4. Statistical design

Based on these 5 factors, a d-optimal interaction design was selected (MODDE, Version 11.0, Umetrics®, Umeå, Sweden) resulting in 27 experiments including 3 center point experiments (see Table 1).

D-optimal designs are used when a non-standard experimental design needs to be created (e.g. irregular experimental regions, multi-level qualitative factors or a combination of process and mixture factors). In this design, the constraints resulted from the fact that only specific combinations of factors 1, 2 and 3 (i.e. specific combinations of score values) could be selected since these factors represent the overarching filler properties which could not be chosen arbitrarily. Figure 2 demonstrates how the numerical values of the DoE factors (which are the score values of the principal components) were derived from the PCA scores plot. As shown for Pharmatose 350M as an example, every filler type has specific values for the principal components which results in a fixed combination of DoE factors 1, 2 and 3. A perfect orthogonality, e.g. by combination of score value 1 for factor 1 (PC 1), score value 0 for factor 2 (PC 2) and score value 1 for factor 3 (PC 3) is not possible since this combination does not correspond to a filler.
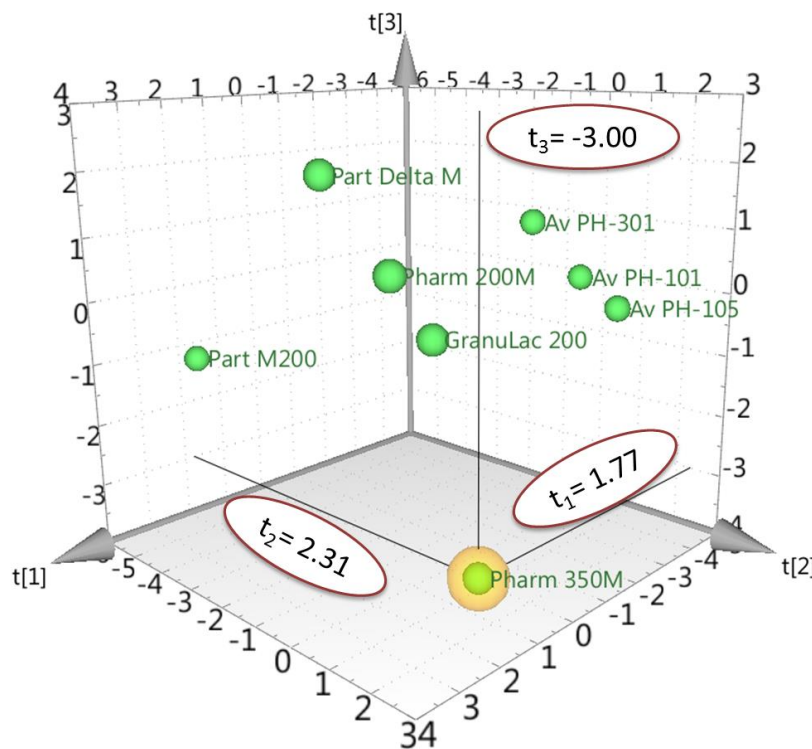
Figure 2. 3-dimensional PCA scores plot of the fillers. Each filler is located in this space according to its overarching properties (PC1, PC2 and PC3). Pharmatose 350M is highlighted as an example. Its t_1, t_2 and t_3 are the score values to be used as DoE factor values for Pharmatose 350M.

By applying the selected d-optimal design, the experiments were defined in a way that the factor ranges were maximally covered [13]. The asset of this d-optimal design was that the factors 1, 2 and 3 (which represent the fillers score values of the overarching properties) enabled to link the DoE with the original

filler PCA model and underlying filler data set in order to understand the impact of filler properties upon the pCQAs of granules and tablets, being responses of the DOE (see further). A limitation of the selected design was that confounding partially occurred between 2-factor interaction terms as well as between main factor and 2-factor interaction terms. However, no confounding above the default threshold of 0.3 was present between the main model terms [14]. Confounding of factors can be attributed to a deviation from perfect orthogonality of the factors and impedes the assignment of an observed effect to one of the confounded factors. The DOE responses which were selected for the statistical model are described in detail in section 2.4.

2.2.5. Experimental runs

Table 1 provides an overview of the experiments. The center point was run in triplicate (experiment number 19-21).

Table 1. DoE design matrix

Experiment number (not run order)	Filler type	Binder type (factor 4)	Binder concentration in granules (factor 5)	Filler principal component 1 (factor 1)	Filler principal component 2 (factor 2)	Filler principal component 3 (factor 3)
1	Avicel PH301	Kollidon	1.5%	-3.37	-0.70	0.98
2	Avicel PH105	Pharmacoat	1.5%	-3.84	1.14	-0.30
3	Avicel PH301	Pharmacoat	2.0%	-3.37	-0.70	0.98
4	Avicel PH301	Kollidon	1.0%	-3.37	-0.70	0.98
5	Parteck M200	Pharmacoat	1.0%	1.83	-5.56	-1.18
6	Avicel PH105	Pharmacoat	2.0%	-3.84	1.14	-0.30
7	Avicel PH105	Kollidon	1.0%	-3.84	1.14	-0.30
8	Granulac 200	Pharmacoat	1.0%	2.20	1.71	0.21
9	Avicel PH101	Kollidon	2.0%	-4.31	-0.14	0.02
10	Parteck M200	Pharmacoat	2.0%	1.83	-5.56	-1.18
11	Parteck M200	Kollidon	1.0%	1.83	-5.56	-1.18
12	Parteck Delta M	Pharmacoat	2.0%	2.76	-0.28	2.18
13	Parteck Delta M	Kollidon	1.0%	2.76	-0.28	2.18
14	Pharmatose 200M	Kollidon	1.0%	2.94	1.51	1.09
15	Pharmatose 350M	Pharmacoat	1.0%	1.77	2.31	-3.00
16	Pharmatose 350M	Pharmacoat	2.0%	1.77	2.31	-3.00
17	Pharmatose 350M	Kollidon	1.0%	1.77	2.31	-3.00
18	Pharmatose 350M	Kollidon	2.0%	1.77	2.31	-3.00

19	Avicel PH301	Pharmacoat	1.5%	-3.37	-0.70	0.98
20	Avicel PH301	Pharmacoat	1.5%	-3.37	-0.70	0.98
21	Avicel PH301	Pharmacoat	1.5%	-3.37	-0.70	0.98
22	Avicel PH101	Pharmacoat	1.0%	-4.31	-0.14	0.02
23	Parteck Delta M	Pharmacoat	1.0%	2.76	-0.28	2.18
24	Granulac 200	Kollidon	2.0%	2.20	1.71	0.21
25	Parteck Delta M	Kollidon	2.0%	2.76	-0.28	2.18
26	Parteck M200	Kollidon	2.0%	1.83	-5.56	-1.18
27	Pharmatose 200M	Pharmacoat	2.0%	2.94	1.51	1.09

2.3. Manufacturing of DoE batches

The DoE batches were manufactured via continuous twin screw wet granulation followed by fluid bed drying (using a six-segmented fluid bed dryer). The tablet compression of the dried granulate was performed in batch mode after addition of the extra-granular phase. Granules and tablets were characterized via IPC tests. Figure 3 provides an overview of the process flow, including the IPC tests that were performed for granules and tablets.
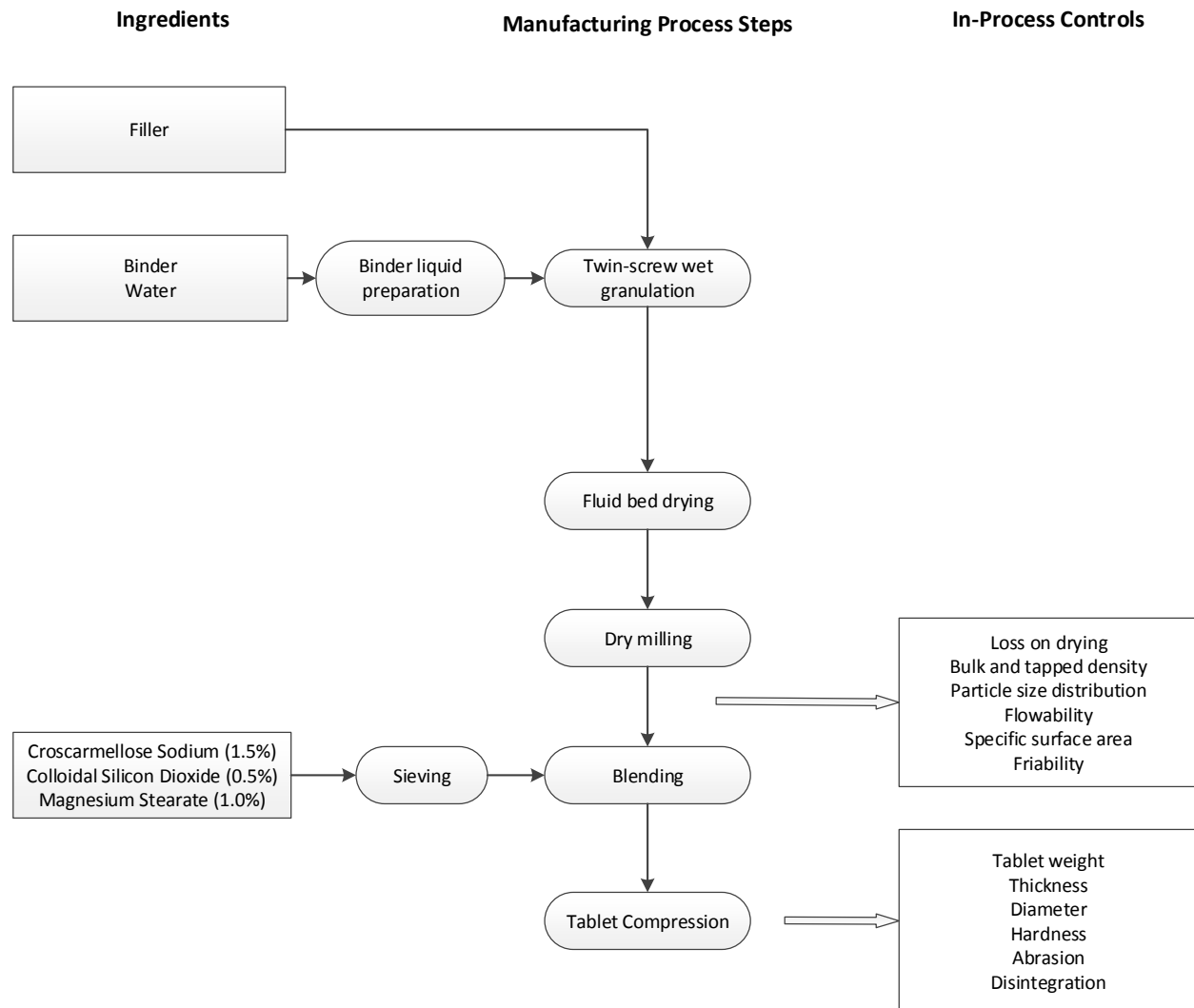
Figure 3. Process flow chart for the manufacturing of DoE batches including IPC tests

2.3.1. Granulation

The ConsiGma®-25 technology (GEA Pharma Systems, Collette®, Wommelgem, Belgium) was used for the manufacturing of the granules. This technology consisted of a twin screw granulator linked to a six-segmented fluid bed dryer and a granule conditioning unit with a cone mill [15].

Process parameters setting for granulation

Since the objective of this study was to understand the influence of the formulation composition on the product and process performance it was important to minimize the influence of process variables as well as of raw material variability on granule quality. Therefore, the same lots of excipients were used throughout the DoE study. Also the process parameters were set to the same fixed values wherever

possible. Granulation was conducted at a granulation jacket temperature of 25 °C. The temperature of the inlet air in the fluid bed dryer was set to 50 °C. For dry milling of the granules a sieve size of 1.575 mm and a rotating speed of 1000 rpm was used. For all experiments a screw configuration of 2x6 kneading elements in an angle of 60° was used, while a block of 6 kneading elements was positioned after each liquid entry port in the granulation barrel (Figure 4). Binder liquid was added via the first and water via the second entry port of the barrel. Although the viscous binder liquid and water were separately added during granulation, the miscibility of both phases in the granulation barrel was visually confirmed during pre-trials with coloured binder liquid (data not shown).
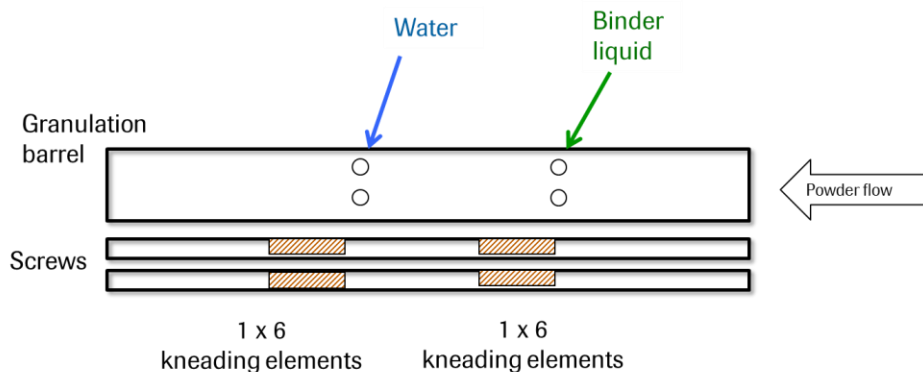

Figure 4. Scheme of the position of the liquid addition ports and kneading elements in the granulation barrel

Other granulation parameters, however, were adjusted due to variations in formulation composition in order to avoid under- or over-granulation and to obtain a proper product. Especially the water content needed for wet granulation varied depending on the filler type in the formulation. A systematic approach for the selection of the most appropriate settings was applied for the parameters "water content" and "screw speed" in order to ensure optimal granulation conditions for each formulation: prior to the manufacturing of a batch, first, the appropriate water content and secondly, the optimal screw speed was identified. For the identification of the appropriate water content, granules were produced at a fixed screw speed setting and granule samples were collected at different water contents, starting from very dry and powdery granules and increasing the water content stepwise until granules were over-wetted. The collected granule samples were visually examined with regard to particle size and examined by hand regarding their state of agglomeration and binding. The binder liquid feeding system (Figure 5) was set-up to ensure consistent binder concentration in the formulation as it was possible to adjust the water flow rate independently of the granulation liquid flow rate. Once the most appropriate setting for "water content" was identified, in a next step the screw speed was adjusted accordingly to optimize the granule particle size, where needed. The decision on acceptable granule size was taken based on operator experience and the objective was to achieve comparable wet granule sizes for all manufactured batches. Powder mass feed rate and binder liquid feed rate were selected to reach the target binder concentration in the formulation. The ratio of powder feed rate over screw speed was kept constant at 0.02 (e.g. 10 kg/h powder mass flow over 500 rpm screw speed) for all batches to achieve a consistent barrel filling degree. Table 2 provides an overview of the applied granulation process parameters L/S ratio, throughput filler and screw speed per batch.

Table 2. Applied process parameters per batch during granulation

Experiment number	Filler type	Binder type	Binder concentration in granules	L/S ratio	throughput filler (kg/h)	screw speed (rpm)
1	Avicel PH301	Kollidon	1.5%	0.43	10	500
2	Avicel PH105	Pharmacoat	1.5%	0.90	10	500
3	Avicel PH301	Pharmacoat	2.0%	0.49	11	500
4	Avicel PH301	Kollidon	1.0%	0.45	13	600
5	Parteck M200	Pharmacoat	1.0%	0.21	13	600
6	Avicel PH105	Pharmacoat	2.0%	0.79	11	500
7	Avicel PH105	Kollidon	1.0%	0.75	13	600
8	Granulac 200	Pharmacoat	1.0%	0.10	13	600
9	Avicel PH101	Kollidon	2.0%	0.59	11	500
10	Parteck M200	Pharmacoat	2.0%	0.20	11	500
11	Parteck M200	Kollidon	1.0%	0.21	13	600
12	Parteck Delta M	Pharmacoat	2.0%	0.11	11	500
13	Parteck Delta M	Kollidon	1.0%	0.10	13	600
14	Pharmatose 200M	Kollidon	1.0%	0.07	13	600
15	Pharmatose 350M	Pharmacoat	1.0%	0.10	13	600
16	Pharmatose 350M	Pharmacoat	2.0%	0.07	11	500
17	Pharmatose 350M	Kollidon	1.0%	0.08	13	600
18	Pharmatose 350M	Kollidon	2.0%	0.08	11	500
19	Avicel PH301	Pharmacoat	1.5%	0.48	10	500
20	Avicel PH301	Pharmacoat	1.5%	0.50	10	500
21	Avicel PH301	Pharmacoat	1.5%	0.50	10	500
22	Avicel PH101	Pharmacoat	1.0%	0.84	13	600
23	Parteck Delta M	Pharmacoat	1.0%	0.11	13	600
24	Granulac 200	Kollidon	2.0%	0.06	11	500
25	Parteck Delta M	Kollidon	2.0%	0.10	11	500
26	Parteck M200	Kollidon	2.0%	0.18	11	500
27	Pharmatose 200M	Pharmacoat	2.0%	0.09	11	500
28	Avicel PH101	Kollidon	1.0%	0.67	13	600
29	Avicel PH101	Pharmacoat	2.0%	0.55	11	500
30	Parteck M200	Pharmacoat	1.5%	0.19	10	500
31	Pharmatose 350M	Pharmacoat	1.5%	0.09	10	500

The drying time in the fluid bed dryer was adjusted to reach a target LOD (loss on drying) of the granules which corresponded to the original LOD of the filler in the formulation. This approach was used in order to obtain a residual moisture in the granules which is in equilibrium at ambient conditions. The target LOD was defined as 0.5-1.0% for lactose and mannitol and 3.0-4.0% for microcrystalline cellulose. The inlet airflow was adjusted to ensure optimal fluidization conditions to account for the varying weight of granules depending on the water content that was used for granulation. The binder liquid was fed to the granulation barrel using peristaltic pumps. Tubings with inner diameters varying from 1.6 to 6.4 mm were selected as appropriate for the water and binder liquid addition in order to reach the target feed rate. Nozzles with diameters of 0.8 to 2.4 mm were applied to guarantee a constant liquid flow at the target liquid feed rate.
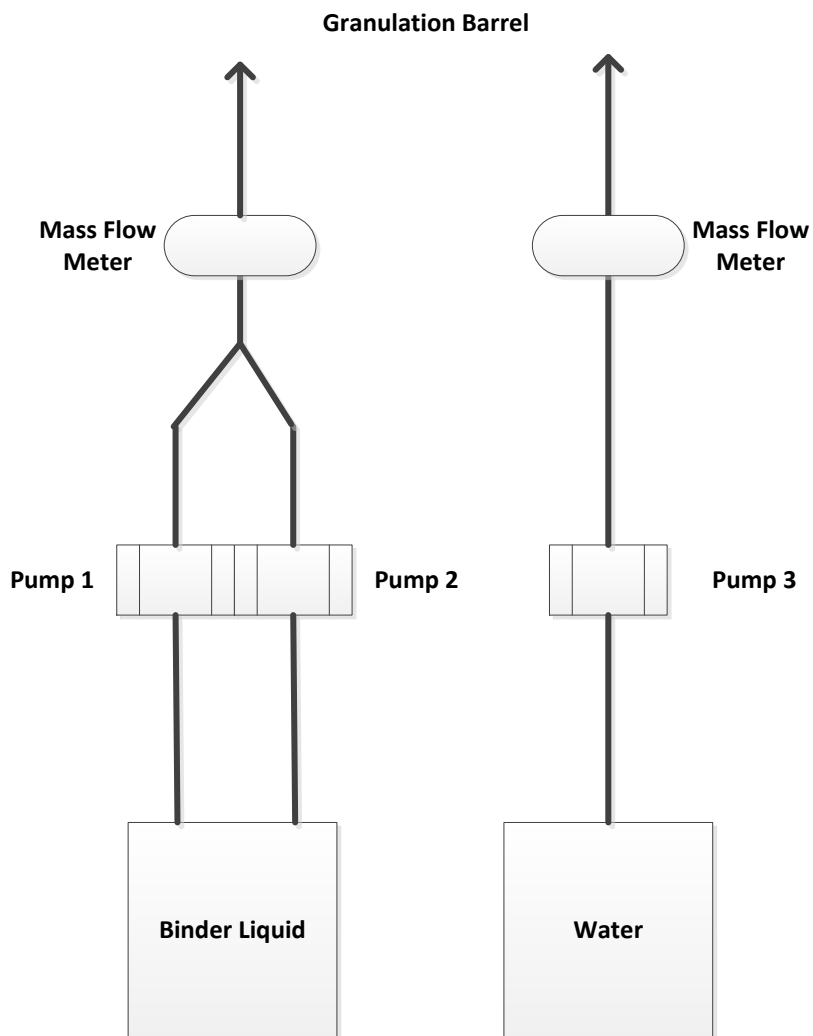

Figure 5. Scheme for set-up of binder liquid and water addition

2.3.2. Final blend preparation

Extragranular phase was added to the granules prior to tablet compression. 0.5% silicon dioxide, 1.5% croscarmellose sodium and 1.0% magnesium stearate were selected as extragranular excipients for all DoE batches. Silicon dioxide was added to provide sufficient flowability to the blend, magnesium stearate was selected as most common lubricant to ensure smooth tablet compression and prevent sticking. Croscarmellose sodium was added for adequate tablet disintegration. A croscarmellose concentration of 1.5% was selected in order not to overrule the effects of the formulation composition on disintegration time and secondly, obtain disintegration times which were in a realistic range according to pharmacopoeial requirements. Silicon dioxide and croscarmellose sodium were sieved (1.0 mm mesh size) and mixed with the milled granules in a tumble blender (Turbula T10B, Willy A. Bachofen, Muttenz, Switzerland) at 24 rpm for 5 minutes. Magnesium stearate was sieved (1.0 mm mesh size), added to the blend and further mixed for 3 minutes.

2.3.3. Tablet compression

Tablet compression parameters were fixed for all batches in order to minimize their influence on the tablet characteristics. Tablets were compressed using a rotary press (Korsch XL200, Berlin, Germany) which was equipped with 4 pairs of 9 mm flat-faced punches running at 30 rpm. Tablets with a mass of 300 mg were compressed at forces of 8, 15 and 22 kN. In addition, tablets with a target hardness of 75 N were compressed for each batch in order to allow comparison of tablet attributes at a standardized hardness.

2.3.4. Characterization of granule attributes

Samples of the produced granules were collected per batch and characterized by the test methods described below.

Particle Size Distribution
The particle size of granules was analysed using sieve analysis. Sieves of 1400, 1000, 710, 500, 355, 250, 180, 125 and 90 µm were used. A motion amplitude of 2mm (continuous mode) was applied for 5 minutes. The sample size was 100 g. The median particle size $D63.2$ in µm was calculated based on mass according to the Weibull distribution. Moreover the fine fraction was calculated as % of granules below 125 µm, the yield fraction as % of granules between 125 and 710 µm, and the coarse fraction as % of granules above 710 µm.

Bulk and tapped density
The volume of 100 g granules after 0 taps ($volume_{bulk}$) and 1250 taps ($volume_{tapped}$) was determined using a tapping machine (J. Engelsmann, Ludwigshafen a. Rhein, Germany). Considering the sample mass, bulk density ($mass/volume_{bulk}$ in g/ml) and tapped density ($mass/volume_{tapped}$ in g/ml) were calculated as well as the Hausner Ratio ($density_{tapped}/density_{bulk}$) [16].

Flowability
Flowability of granules was characterized by means of ring shear testing (Ring Shear Tester RST-XS, Dr. Dietmar Schulze, Wolfenbüttel, Germany) applying a pre-shear of 1000 Pa. The three most suitable

normal loads were chosen automatically for each measurement by the device, whereas the first normal load was repeated as a fourth normal load measurement point. The flow function coefficient (ffc), which is the ratio of consolidation stress to unconfined yield strength, was calculated [17].

Moisture content

A halogen moisture analyser (Mettler Toledo HR83, Mettler-Toledo, Greifensee, Switzerland) was used to measure loss on drying (LOD) (n=1, in %) at a drying temperature of 90°C until the weight variation was below 2 mg within 30 sec.

Specific Surface Area (BET method)

In the validity range of the BET-isotherm, the specific surface area (in m^2/g) was measured by means of nitrogen adsorption (Tristar II 3020, Micrometrics, Norcross, USA) (n=2). Prior to measurements, the samples were over-night degased at vacuum.

Friability

The friability of granules was measured using a friability tester (PTF E Pharma Test, Hainburg, Germany) as described by Vercruysse et al. [18]. The fine fraction of the granules was removed prior to the measurements using a 250 μm sieve. Afterwards 10.0 g of the granules (I_{wt}) were filled into the drum together with 200 glass beads of 4 mm diameter. At a speed of 25 rpm a 10 minute run was performed. The generated granule size fraction below 250 μm was again removed and the residual amount of granules was weighed (F_{wt}). The friability was calculated as $((I_{wt} - F_{wt})/I_{wt}) * 100$ in %.

2.3.5. Characterization of tablet attributes

Tablet mass, height, diameter and hardness were measured for 8, 15 and 22 kN compression forces as well as for the samples with a target hardness of 75 N. Additionally, disintegration time and abrasion were determined for tablets with 75 N target hardness.

Tablet hardness and solid fraction

Tablet thickness, diameter, weight and hardness were determined for a sample of 10 tablets processed at each compression force as well as the 75 N hardness samples with an automatic tablet testing system (Sotax HT 100, Sotax, Aesch, Switzerland). Tablet solid fraction was calculated from tablet mass (m in g), volume (V in cm^3) and true density (ρ_{true} in g/cm^3) as $(m/V)/\rho_{true}$. True density of the final blend before compression was measured using a helium pycnometer (AccuPyc 1330, Micrometrics, Norcross, USA). Five purges at 19.5 psig and five runs at 19.5 psig were conducted in one measurement (n=2).

Abrasion

100 g of de-dusted tablets (m_1 in g) with target hardness of 75 N were filled into a Weis-Fogh drum (Friabilator AE-1, Biomation, Jugenheim, Germany) which rotated 1250 times at a speed of 100 rpm. After the stress test, tablets were de-dusted again, the remaining tablet weight was determined (m_2 in g) and abrasion (in %) was calculated as $((m_1-m_2)/m_1)*100$.

Disintegration

The disintegration time (in sec) of the 75 N target hardness tablets (n=6) was determined using a disintegration tester (basket method; Sotax DT2, Sotax AG, Aesch, Switzerland) with automatic endpoint detection. Demineralized water with a temperature of 37°C was used as disintegration medium.

Compression force

The compression force (in kN) which was needed to reach a target tablet hardness of 75N was recorded and used as an indirect measure for tablet hardness.

2.4. DoE analysis and model development

The above-described granule and tablet attributes were used as DoE responses (see Table 3).

Table 3. List of granule and tablet model responses

Granule responses	Tablet responses
Bulk density	Disintegration time
Tapped density	Tablet abrasion
Hausner ratio	Solid fraction of tablets with 75 N hardness
Particle size D63.2	Compression force needed to reach 75 N target tablet hardness
Fine fraction <125 µm	Ejection force at 15 kN compression force
Yield fraction 125-710 µm	
Coarse fraction 710-1400 µm	
Flowability	
Friability	
Specific surface area	
Torque granulation barrel	

Multiple linear regression (MLR) models were fitted for each response using Modde (Version 11.0, Umetrics®, Umeå, Sweden). Responses were thus studied independently from each other. A logarithmic transformation of responses was performed if needed in order to convert a non-normal into a normal distribution since the latter is a general requirement for linear regression [14]. Orthogonally scaled and centred variables were used in the coefficient plots to achieve comparability of factors.

The models were fitted and optimized for two purposes. First, the models were fitted with main model terms in order to understand which factors (i.e. the formulation properties) influence the responses (i.e. granule and tablet properties) (see section 3.3.1). Although the statistical design allowed the inclusion of interaction model terms, it was not beneficial for this purpose to include interaction model terms due to confounding among the main and interaction model terms. Second, the models were fitted for prediction and model verification purpose. Here the addition of interaction model terms can be beneficial to improve the model fit. The models were optimized by removing statistically insignificant model terms as long as this resulted in larger Q^2 values [6] (results see sections 3.2 and 3.4). As specific parameters (i.e. inlet air flow in the fluid bed dryer, LOD of dry granules and inlet air humidity in the fluid bed dryer) introduced

uncontrolled variability during the experiments, these parameters were added to the DoE as uncontrolled factors (one uncontrolled factor at a time).

3. Results and Discussion

3.1. Process performance

A total of 31 formulations (27 DoE batches plus 4 batches for external model verification purpose, see Table 1 and Table 7) were manufactured via continuous wet granulation in this study.

Typically formulations designed for wet granulation processes consist of a blend of multiple fillers (e.g. two complementary fillers like MCC and lactose). In this study, however, formulations in their most simple form were used with the objective to obtain more pronounced effects of the different filler types on the product characteristics. For the majority of batches, no manufacturing issues were observed as appropriate granules and tablets could be produced. During wet granulation, limitations were observed when processing formulations with Avicel PH301 as filler. Although these formulations yielded granules, the granulator had to be restarted several times as the process was automatically interrupted when the maximum screw torque was exceeded. This observation might be attributed to the higher density of Avicel PH301 compared to the two other Avicel grades since the density is the property which is different for Avicel PH301 compared to Avicel PH105 and PH101. This observation is in contrast to the expectation that the higher density of Avicel PH301 results in a lower filling degree of the granulation barrel which might result in a reduced screw torque. Potentially, despite the differences in the overall barrel filling degree for the Avicel grades according to their different densities, comparable filling levels might be achieved in the kneading element area: At the kneading elements (where most friction occurs) the smallest space is available between screw elements and granulation barrel wall which would result in equal amounts of powder for all grades regardless of the powder density. When the space around the kneading elements is fully filled with wetted powder, this would results in a higher mass of Avicel PH301 (due to higher density of Avicel PH301 of 0.433 g/ml compared to Avicel PH101 of 0.308g/ml and Avicel PH105 of 0.313g/ml) which potentially results in higher resistance and friction in the kneading element area and thus in higher screw torque.

As expected, it was more difficult to obtain a stable and consistent granulation liquid flow with increasing viscosity of the binder liquid. Particularly binder solutions with a high viscosity (e.g. for formulations with 2% HPMC binder concentration) required a suitable selection of tubing size and assessment of appropriate pump speed with pre-trials in order to ensure a consistent flow at the target binder liquid flow rate. Although the majority of batches showed a reasonable to good tablet compression performance (maximal observed ejection force of approx. 360 N), some formulations were limited in the process performance during tablet compression. For batch 15 (Pharmatose 350M + 1% Pharmacoat) and batch 31 (Pharmatose 350M + 1.5% Pharmacoat; one of the model verification batches, see section 3.4) high ejection forces (up to 1600 N) were observed. Batch 31 did not allow to compress tablets at 15 kN compression force or higher since tablets broke during ejection from the die. However, batches with Pharmatose 350M + 2% Pharmacoat or with Kollidon (at any concentration) could be processed into tablets without difficulties.

Some formulations revealed sticking tendencies (Batch 5, 10, 15, 17) or showed lamination at 22 kN compression force (batch 2, 6, 7). The three latter formulations for which lamination was observed at 22kN, contained Avicel PH105 as filler. Although MCC undergoes plastic deformation during compression, it was assumed that the high compression force of 22 kN at a tablet weight of 300 mg resulted in over-compression. Over compression (i.e. excessive compaction pressure) during tabletting causes a flattening out of granules which reduces the bonding-ability due to flat granule surfaces without irregularities [19]. Therefore, the compacts tend to laminate. Avicel PH105 is designed as the most compressible MCC quality among the grades included in this study. Hence, the state of over-compression is expected to be reached at lower compression forces compared to the other MCC grades (Avicel PH101 and PH301) [20].

3.2. Quality of the statistical models

An overview of the model parameters R^2 and Q^2 after model optimization is given in Figure 6.
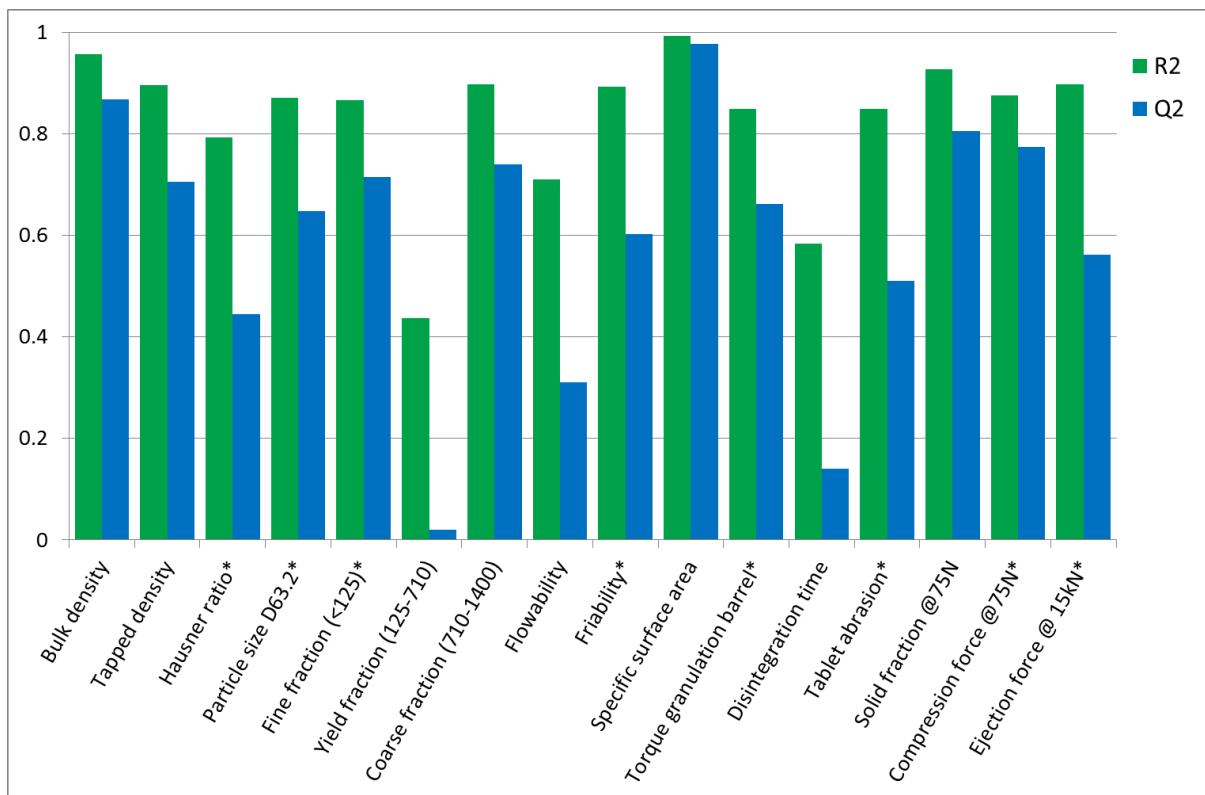
Figure 6. Summary of fit: R^2 (green bars) and Q^2 (blue bars) of the optimized models (the * indicates that the response was log transformed)

R^2 is an indicator for the model fit and describes how well the variation in a response can be explained by the model terms. The closer the value is to 1, the better the model fit is. Overall the models had a good fit (R^2) for all responses. However, assessment of model quality should also take Q^2 into account which indicates the predictive power of the model. Q^2 is defined as $1 - (\frac{PRESS}{SS_{tot}})$ where *PRESS* is the prediction residual sum of squares calculated based on all model samples and SS_{tot} is the total sum of squares of the responses [14]. A $Q^2 > 0.5$ generally indicates that the model has a good predictive power. The model predictability is further discussed in section 3.4.

For all responses (except for disintegration time) a good reproducibility was obtained since the variation of the center point experiments per response was low and much smaller than the overall variability of the DoE experiments. An example for a replicate plot is shown in Figure 7.

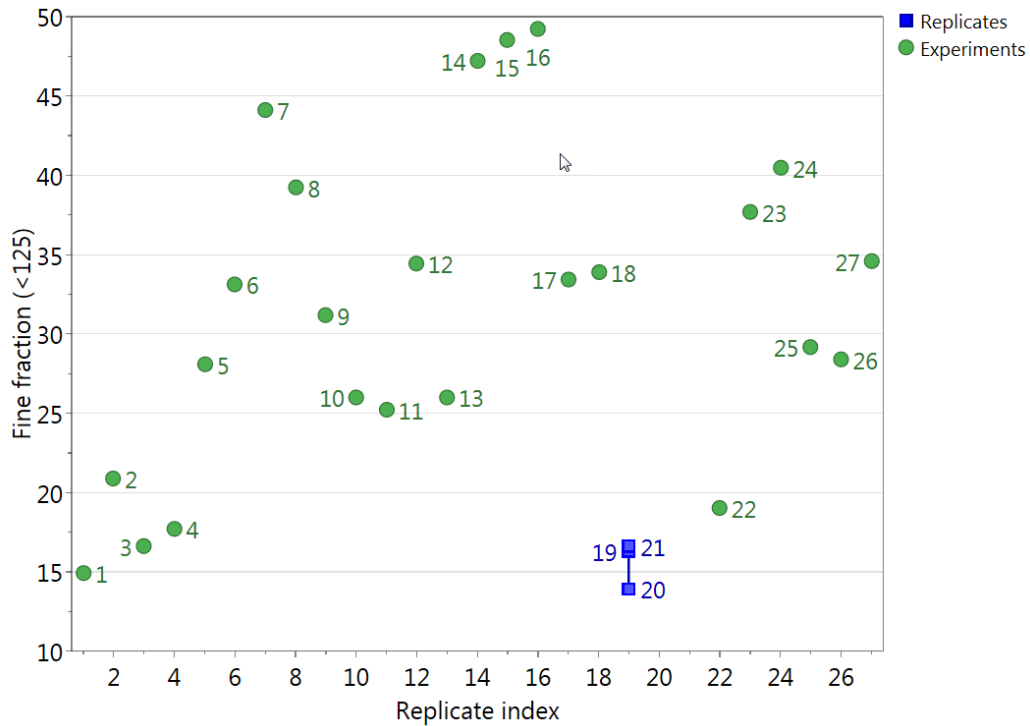**Figure 7. Replicate plot of the response "Fine fraction" of granules. Replicates are highlighted in blue (number 19, 20 and 21)**

In this study, it was observed that the variation of factors in the defined experimental space resulted in relevant variation of the granule and tablet characteristics for the majority of responses (Table 4), which was a good foundation to obtain meaningful quality models.

Table 4. Numerical values of granule and tablet responses for the DoE runs. (*measurement values are missing)

Experiment number	Filler type	Binder type	Binder concentration in granules	Bulk density (in g/ml)	Tapped density (in g/ml)	Hausner ratio	Particle size D63.2 (in µm)	Fine fraction (<125 µm) (in %)	Yield fraction (125-710 µm) (in %)	Coarse fraction (710-1400 µm) (in %)	Flowability (ffc)	Friability (in %)	Specific surface area (in m²/g)	Torque granulation barrel (in Nm)	Disintegration time (in sec)	Tablet abrasion (in %)	Solid fraction @75N	Compression force @75N (in kN)	Ejection force @15kN (in N)
1	Avicel PH301	Kollidon	1.5%	0.57	0.68	1.19	594	14.9	55.6	29.5	4.4	2	0.4	4.7	36	0.4	0.81	7.5	46
2	Avicel PH105	Pharmacoat	1.5%	0.53	0.64	1.21	454	20.9	59.8	19.4	5.4	7	1.0	3.3	24	0.6	0.79	6.5	38
3	Avicel PH301	Pharmacoat	2.0%	0.63	0.75	1.19	587	16.6	53.6	29.9	7.0	3	0.4	11.1	217	0.5	0.89	15.0	44
4	Avicel PH301	Kollidon	1.0%	0.61	0.75	1.23	550	17.7	55.7	26.6	3.6	3	0.5	8.4	169	1.0	0.88	15.0	47
5	Parteck M200	Pharmacoat	1.0%	0.56	0.63	1.13	373	28.1	55.9	15.7	4.0	10	3.3	2.1	93	0.4	0.82	9.5	365
6	Avicel PH105	Pharmacoat	2.0%	0.53	0.68	1.28	366	33.1	51.3	15.7	5.4	6	1.0	3.3	103	0.8	0.80	7.0	43
7	Avicel PH105	Kollidon	1.0%	0.48	0.66	1.38	281	44.1	43.2	12.6	3.5	9	1.0	3.2	88	1.0	0.80	7.0	42
8	Granulac 200	Pharmacoat	1.0%	0.6	0.69	1.15	284	39.2	50.2	10.6	4.3	24	0.5	2.1	97	0.7	0.86	13.0	158
9	Avicel PH101	Kollidon	2.0%	0.45	0.56	1.24	420	31.2	47.3	21.7	10.2	4	1.0	3.6	19	0.8	0.73	5.0	39
10	Parteck M200	Pharmacoat	2.0%	0.55	0.62	1.13	384	26.0	57.7	16.2	4.2	9	3.3	2.0	113	0.2	0.80	8.0	80
11	Parteck M200	Kollidon	1.0%	0.57	0.64	1.12	422	25.2	54.2	20.4	4.1	7	2.9	2.8	119	0.2	0.79	7.0	113
12	Parteck Delta M	Pharmacoat	2.0%	0.51	0.65	1.27	360	34.4	50.8	15.0	4.6	8	0.6	1.8	94	0.8	0.82	8.0	168
13	Parteck Delta M	Kollidon	1.0%	0.51	0.6	1.18	445	26.0	51.7	22.0	4.3	4	0.8	3.6	114	0.6	0.83	7.0	62
14	Pharmatose 200M	Kollidon	1.0%	0.53	0.64	1.21	202	47.2	47.3	5.6	2.8	18	0.2	1.7	106	0.5	0.88	15.0	92
15	Pharmatose 350M	Pharmacoat	1.0%	0.55	0.66	1.20	207	48.5	46.9	4.6	2.4	66	0.4	1.4	104	*	0.86	22.0	1378
16	Pharmatose 350M	Pharmacoat	2.0%	0.56	0.65	1.16	210	49.2	45.7	5.0	3.7	28	0.4	1.3	161	0.5	0.85	11.0	129
17	Pharmatose 350M	Kollidon	1.0%	0.53	0.63	1.19	253	33.4	58.0	8.5	2.8	18	0.3	3.1	104	1.3	0.87	15.0	87
18	Pharmatose 350M	Kollidon	2.0%	0.56	0.64	1.14	351	33.9	49.7	16.2	6.4	11	0.4	3.0	160	0.5	0.83	9.0	119
19	Avicel PH301	Pharmacoat	1.5%	0.6	0.71	1.18	556	16.3	56.5	27.2	*	2	0.4	5.7	248	0.5	0.88	14.0	45
20	Avicel PH301	Pharmacoat	1.5%	0.62	0.74	1.19	643	13.9	52.4	33.7	6.0	5	0.4	10.1	210	0.5	0.89	14.0	43
21	Avicel PH301	Pharmacoat	1.5%	0.63	0.74	1.17	553	16.6	57.1	26.3	6.0	3	0.4	8.1	153	0.5	0.88	14.5	46
22	Avicel PH101	Pharmacoat	1.0%	0.52	0.62	1.19	537	19.0	53.5	27.7	3.7	1	1.1	3.4	142	0.6	0.83	10.0	51
23	Parteck Delta M	Pharmacoat	1.0%	0.49	0.58	1.18	281	37.7	52.7	9.5	3.4	18	0.7	1.4	99	0.5	0.86	10.5	77
24	Granulac 200	Kollidon	2.0%	0.59	0.71	1.20	294	40.5	45.8	13.6	5.2	15	0.5	1.4	177	0.7	0.82	8.0	176
25	Parteck Delta M	Kollidon	2.0%	0.52	0.6	1.15	490	29.2	44.9	25.9	2.2	1	0.5	4.6	161	0.7	0.81	6.5	195
26	Parteck M200	Kollidon	2.0%	0.57	0.65	1.14	421	28.4	51.1	20.4	6.4	5	2.7	3.2	168	0.2	0.76	5.5	176
27	Pharmatose 200M	Pharmacoat	2.0%	0.58	0.68	1.17	305	34.6	53.7	11.6	5.1	17	0.3	1.6	266	0.6	0.87	11.5	118

3.3. Impact of studied factors on granule and tablet responses

In order to avoid confounding in the model terms (see above), linear models with main model terms only were selected to evaluate if, and to what extent, the studied factors (i.e. fillers overarching properties, binder type and concentration) had an impact on the responses (i.e. granule and tablet properties) (see section 2.4). The results which are discussed in section 3.3 are based on the main term models. A list of the effects per response is given in Table 5.

Table 5. Overview of main term model effects for untransformed responses (remark: no information on statistical significance is provided in this table; for statistical significance of factors see Table 6)

Response	Filler PC1 (factor 1)	Filler PC2 (factor 2)	Filler PC3 (factor 3)	Binder type (factor 4)	Binder concentration (factor 5)
Bulk density	0.00	-0.01	0.00	-0.02	0.01
Tapped density	-0.01	0.00	0.00	-0.02	0.01
Hausner ratio	-0.02	0.02	0.01	0.02	0.00
Particle size D63.2	-53.59	-39.72	55.35	12.22	33.34
Fine fraction (<125)	4.05	3.97	-3.49	0.33	-0.79
Yield fraction (125-710)	-0.69	-1.43	-0.12	-2.74	-1.86
Coarse fraction (710-1400)	-3.41	-2.50	3.65	2.37	2.71
Flowability	-0.51	-0.18	-0.02	0.26	1.96
Friability	3.83	4.15	-7.05	-8.07	-7.22
Specific surface area	0.05	-0.67	-0.35	-0.08	-0.06
Torque granulation barrel	-1.08	-0.27	0.81	0.18	0.34
Disintegration time	5.36	0.89	9.82	-21.95	34.73
Tablet abrasion	-0.02	0.13	-0.01	0.10	-0.11
Solid fraction @75N	0.00	0.01	0.01	-0.03	-0.03
Compression force @75N	0.16	1.08	-0.74	-3.02	-3.59
Ejection force @ 15kN	50.62	22.17	-115.47	-120.96	-118.73

3.3.1. Overview: impact of factors on responses

The coefficient plot (Figure 8) displays the factors' regression coefficients per response including 95% confidence intervals. The coefficients reflect the change in the response when a factor is varied from its average setpoint to its high setpoint while keeping the other factors at their center point. The confidence intervals indicate whether the coefficients can be considered statistically different from zero. These statistically insignificant terms can be removed from the model during model optimization.
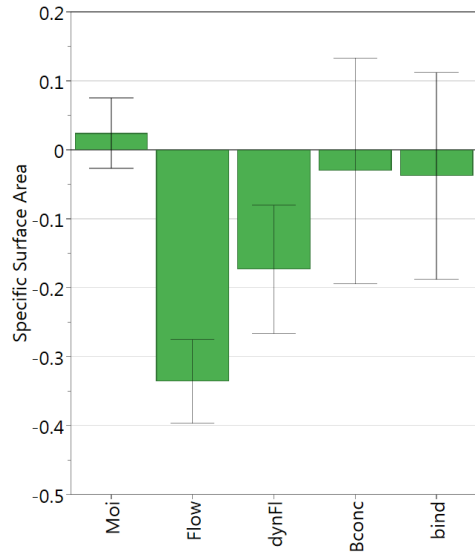
Figure 8. Coefficient plot for the response specific surface area: Increasing the factors "flow-related properties (PC2)" and "dynamic flow (PC3)" resulted in a reduction of granule specific surface area

Table 6. Overview of the factor impacts on responses: arrows in green indicate a significant and pharmaceutically relevant impact, arrows in black indicate a significant but pharmaceutically not relevant impact (models with main model terms were used for this table)

Response	PC1 (moisture-related)	PC2 (flow-related)	PC3 (dynamic flow & others)	Binder concentration	Binder type
Particle size D63.2	↓	↓	↑	---	---
Fine fraction	↑	↑	---	---	---
Yield fraction	---	↓	---	---	---
Coarse fraction	↓	↓	↑	---	---
Bulk density	---	---	---	---	---
Tapped density	---	---	---	---	---
Hausner ratio	↓	↑	---	---	---
Flowability	↓	---	---	↑	---
Friability	↑	↑	↓	(↓) borderline	↓
Specific surface area	---	↓	↓	---	---
Disintegration time	---	---	---	---	---
Tablet abrasion	---	↑	---	---	---
Solid fraction @75N	---	↑	---	---	↓
Compression force @75N	---	---	---	↓	↓
Torque granulation barrel	↓	---	---	---	---
Ejection force @ 15kN	↑	---	↓	---	---

Table 6 summarizes the significance and pharmaceutical relevance of the coefficients of the models (with main model terms) for the different responses. The coefficient plots were used to obtain the information which is summarized in the table. Overall, the impact of filler properties on the granule and tablet responses appear to be more dominant compared to the impact of binder type and concentration. Binder type or concentration only revealed a relevant influence on granule flowability (using a higher binder concentration improved granule flowability) and friability (using Kollidon as binder reduced granule friability) as well as on tablet compression force as an indicator for tabletability (a higher binder concentration and Kollidon as binder both resulted in lower compression forces). Among the overarching properties of the fillers, the moisture-related properties (1st PC) and the flow-related properties (2nd PC)

of the fillers showed a dominant impact on the responses compared to the dynamic flow properties of the filler (3rd PC).

3.3.2. Responses without pharmaceutically relevant impact of fillers and binders

The influence of some factors proved to be statistically significant on some responses (bulk and tapped density, Hausner ratio, yield fraction, torque in the granulation barrel, disintegration time and solid fraction). However, the changes in the responses were not considered pharmaceutically relevant (i.e. the impact was significant but the observed change was rated too small to be of practical relevance).

None of the studied factors had a significant influence on the responses bulk and tapped density, respectively. Moreover, limited variation within the response range was obtained for bulk density (0.45-0.63 g/ml) and tapped density (0.56-0.75 g/ml) as well as for solid fraction (0.73-0.89) (Table 4). However, as the experimentally observed values of these responses were within common target ranges (e.g. 0.4-0.7 g/ml for bulk density, 0.6-0.8 g/ml for tapped density and 0.7-0.9 for solid fraction), optimization of those responses is therefore not necessary. Since a change in the formulation factors did not influence these granule and tablet properties, the advantage is that other responses can be optimized while those responses remain within the desired range. Prior to tablet compression, 1.5% of croscarmellose sodium was added to the extra granular phase. This disintegrant concentration was considered sufficient for all manufactured formulations since the tablet disintegration time was below 5 minutes for all batches. This might be the reason why the studied filler and binder properties did not show a significant influence on disintegration time. Furthermore, the addition of a disintegrant might have overruled a potential small influence by fillers and binders. An efficient way of influencing the disintegration time is expected via proper selection of disintegrant type and concentration rather than by varying filler and binder properties.

The screw torque is a resulting process parameter and can thus be considered as a response in the DoE, as it cannot be actively controlled. Especially in view of long runs, a high screw torque might be unfavourable. None of the studied formulation properties significantly affect the screw torque. The only formulations which had an elevated screw torque during processing contained Avicel PH301 (see Table 4).

3.3.3. Factor impact on individual responses

Granule particle size distribution (PSD)

The granule PSD is of high relevance for the downstream process performance and the potential critical quality attributes of the final drug product. The granule PSD has for example an impact on granule flowability and this directly could impact tablet mass and content variation [21], [22]. High fraction of fines can also lead to segregation issues during tablet compression, which might result in content uniformity issues. Furthermore granule PSD can impact the compressibility of the product as well as dissolution performance [23], [24]. Therefore the PSD of the granules is considered as a key response which is often in focus during formulation and process design.

The statistical granule diameter obtained from the Rosin-Rammler distribution function (D63.2) [25] was significantly impacted by the three overarching filler properties: by changing the factors PC1 or PC3 from

their lowest to highest setpoint, the D63.2 changed by 40-55 µm for each factor. As D63.2 is calculated cumulatively, it contains information about the shift in particle size distribution. The models revealed that fillers with high PC1 and/or PC2 score values increased the granules fine fraction (by approx. 4% per factor) and at the same time decreased the amount of coarse granules (by approx. 3% per factor). Fine and coarse fractions were thus anti-correlated.

Figure 9 is derived from the scores plot of the fillers PCA [12] and was supplemented with information from the DoE. It shows that lactose grades yielded smaller D63.2 values, while Avicel PH301 increased D63.2. However, changes in D63.2 were probably mainly attributed to changes in the particle size distribution. This assumption was based on the finding that yield fraction was not impacted in a relevant way (see below), while fine and coarse fraction were impacted by the same factors (PC1, PC2 and PC3) as D63.2. Interestingly, no correlation of D63.2 with the filler water uptake behaviour, filler solubility or filler particle size D50 was observed (graphs not shown). Therefore, it could be concluded that granule particle size was neither affected by the original particle size of the filler nor by its water solubility or water uptake behaviour in the selected experimental set-up. It is expected that at a fixed L/S ratio, excipient properties like particle size and water uptake revealed an effect on granule particle size. In this study, however, the L/S ratio was defined in order to assure effective granulation for each formulation and to avoid over- or under-granulation. The differences in L/S ratio might be the reason that the excipient properties did not show a relevant impact on granule particle size. No relevant formulation impact was observed on the yield fraction: PC2 was the only factor that significantly impacted the yield fraction. However, an increase/decrease of 1.5% yield fraction was not considered relevant. Thus, it was assumed that the yield fraction can mainly be adjusted by granulation process parameters like screw speed instead of changing the formulation parameters.
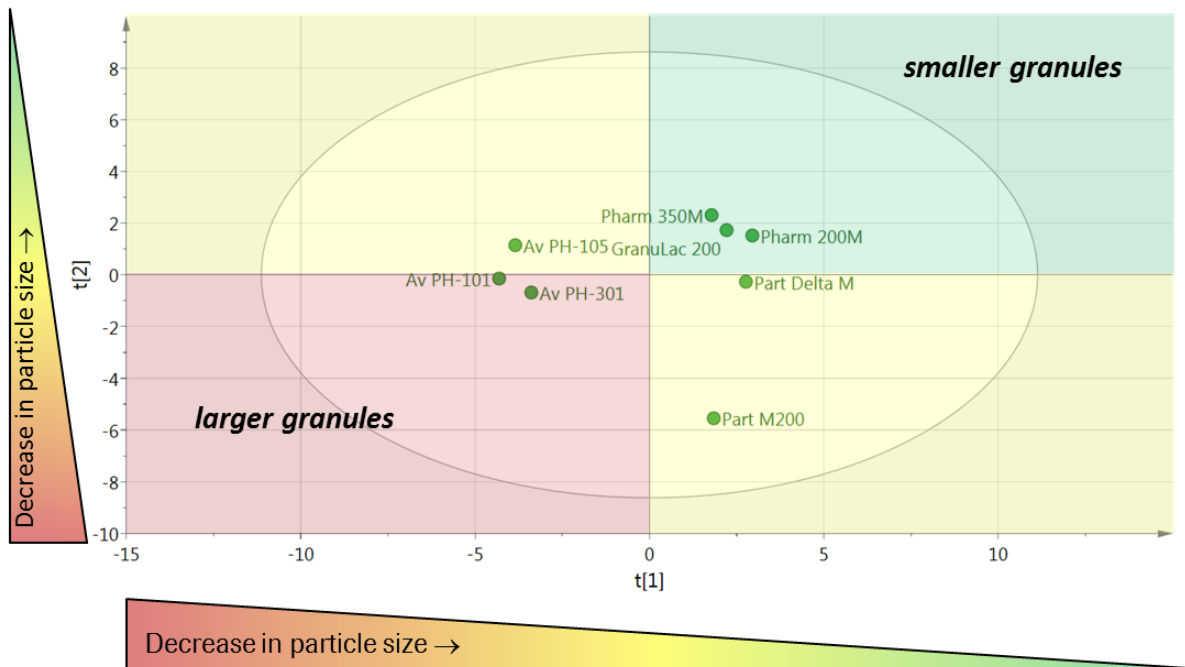

Figure 9. Adopted scores plot from the filler PCA to visualize how the selection of a filler type will influence granule particle size

Granule flowability

The filler properties had a negligible influence on granule flowability (effect of max. 0.5 units), while a higher binder concentration could improve the flowability (effect of 2.0 units) regardless of the binder type that was used. The binder concentration studied in this design ranges from 1-2% and further investigation would be needed to understand if the effect is even more pronounced at higher binder concentrations.

Granule friability

The granule friability was used as indicator for granule strength. Using PVP as binder reduced the granule friability (effect of approx. 8%) and a trend was observed that friability decreased when using higher binder concentrations (effect of approx. 7%). Since all overarching filler properties impacted the granule friability, friability can be substantially lowered by selecting the right filler properties, i.e. a low PC1 and PC2 score values in combination with a high PC3 score value. A correlation (R^2=0.6) was found between the granule fine fraction and friability (Figure 10): friable and therefore weak granules resulted in a higher amount of fines.
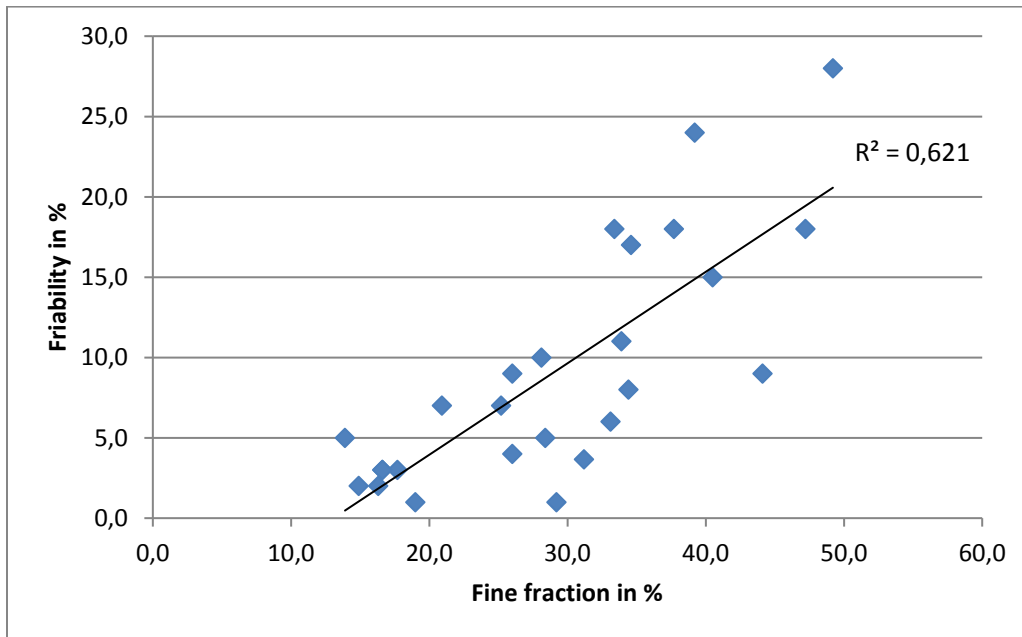

Figure 10. Correlation plot fine fraction (%) vs. friability of granules (%)

Tabletability

The compression force needed to compress tablets to a defined hardness of 75 N was used as an indicator for tabletability. The filler factors did not show a relevant impact on the tablet hardness according to the model, while the binders had a considerable effect. Using PVP as binder as well as higher binder concentrations improved the tabletability, i.e. a lower compression force was needed to reach the target tablet hardness (reduction by approx. 3 kN). In order to better understand why the fillers do not have a relevant effect on the tabletability, the compression force required to reach target hardness was plotted against the filler types, grouped by filler grades (Figure 11).
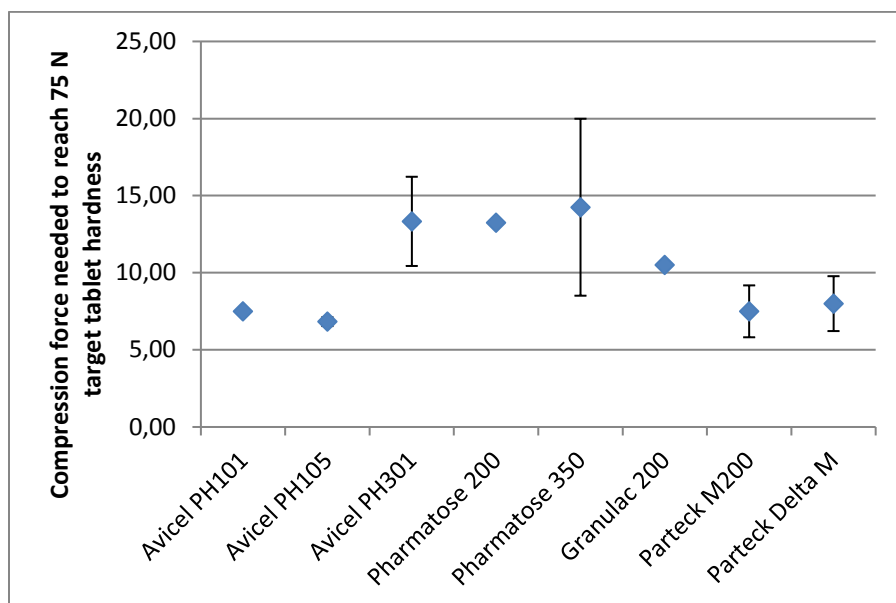
Figure 11. Tabletability (compression force needed to reach target tablet hardness) grouped by filler type. Error bars indicate absolute standard deviation values if available.

Tablets with MCC or mannitol showed a comparable tabletability, while tablets with lactose were inferior considering this response. This observation is in good agreement with previous findings and can be explained with the deformation characteristics of the materials [26]. Avicel PH301, however, shows a significantly lower tabletability compared to other MCC grades, and its tabletability is similar to that of the investigated lactose grades. This observation might be linked to the higher bulk density and lower specific surface area (i.e. reduced surface available for particle bonding) of Avicel PH301 compared to other MCC grades.

Tablet abrasion
PC2 (flow-related properties) was the only factor which showed a relevant impact on tablet abrasion: using Parteck M200 with a low PC2 score value as filler reduced the tablet abrasion (by 0.12%).

Uncontrolled factors
The approach that was used for this study aimed to keep the influence of process parameters on the granule and tablet quality attributes as low as possible to avoid that the impact of formulation parameters (PC1, PC2, PC3 of fillers, binder type and binder concentration) would be overruled by the impact of the process parameters. However, some process parameters needed to be adjusted to account for the different formulation properties (see section 2.4), in order to ensure a good processability. Hence, some process parameters and IPC test results were added – one by one - as uncontrolled factors to the design and their influence upon the studied responses was evaluated. As none of the uncontrolled factors (i.e. inlet air flow, inlet air humidity in the fluid bed dryer and LOD of dry granules) had an impact upon the studied responses, the results confirmed that the necessary adaptations of the process parameters to

account for formulation needs did not significantly influence drug product attributes and that the experimental approach taken in this study was valid.

3.4. Verification of developed DOE models

The purpose of external model verification is to investigate the model applicability for granulation and tabletting experiments with formulations that were not included in the model but that were processed using factor settings within the experimental space. The formulations selected for external model verification are listed in Table 7:

Table 7. Selected formulations for external model verification

Experiment number	Filler type	Binder type (factor 4)	Binder concentration in granules (factor 5)	Filler principal component 1 (factor 1)	Filler principal component 2 (factor 2)	Filler principal component 3 (factor 3)
28	Avicel PH101	Kollidon K30	1.0%	-4.31	-0.14	0.02
29	Avicel PH101	Pharmacoat 603	2.0%	-4.31	-0.14	0.02
30	Parteck M200	Pharmacoat 603	1.5%	1.83	-5.56	-1.18
31	Pharmatose 350M	Pharmacoat 603	1.5%	1.77	2.31	-3.00

As previously described, the models with interaction terms revealed confounding among the factors which impedes to understand which factor is responsible for an observed effect. Nevertheless, the models can be used for predictions. Based on the factor settings of the 4 verification experiments (Table 7), the response values were predicted using the optimized interaction models. These predicted values were compared with the observed experimental values which were generated using the granules and tablets manufactured in the verification runs (Table 8).

Table 8. Observed and predicted values (including confidence intervals) per verification batch (*for batch 31, no tablets with target hardness of 75N could be manufactured as tablets broke during ejection at compression forces above 15kN (see 3.1))

Response	Batch 28 (Avicel PH101 and Kollidon K30)			Batch 29 (Avicel PH101 and Pharmacoat 603)			Batch 30 (Parteck M200 and Pharmacoat 603)			Batch 31 (Pharmatose 350M and Pharmacoat 603)		
	observed experimental value	predicted value	95% confidence interval	observed experimental value	predicted value	95% confidence interval	observed experimental value	predicted value	95% confidence interval	observed experimental value	predicted value	95% confidence interval
Bulk density (in g/ml)	0.46	0.47	0.44 - 0.49	0.45	0.50	0.47 - 0.52	0.54	0.55	0.53 - 0.57	0.52	0.56	0.54 - 0.58
Tapped density (in g/ml)	0.58	0.59	0.55 - 0.63	0.56	0.59	0.55 - 0.63	0.62	0.63	0.59 - 0.66	0.63	0.65	0.63 - 0.68
Hausner ratio	1.26	1.27	1.23 - 1.31	1.24	1.21	1.17 - 1.24	1.15	1.13	1.10 - 1.16	1.21	1.17	1.14 - 1.21
Particle size D63.2 (in µm)	558.4	418.4	335.6 - 521.7	349.4	479.5	392.5 - 585.7	364.5	372.8	312.4 - 444.8	207.2	233.7	196.0 - 278.6
Fine fraction (<125 µm) (in %)	33.3	28.7	23.5 - 35.1	35.0	21.6	18.3 - 25.5	27.4	28.2	23.3 - 34.0	47.5	42.5	35.2 - 51.3
Yield fraction (125-710 µm) (in %)	46.7	52.1	48.9 - 55.3	50.5	53.0	50.5 - 56.1	58.4	55.8	51.6 - 60.1	47.1	48.8	44.0 - 53.6
Coarse fraction (710-1400 µm) (in %)	20.2	22.9	18.4 - 27.5	14.6	25.6	21.5 - 29.7	14.4	15.7	11.9 - 19.5	5.3	6.3	2.5 - 10.1
Flowability (ffc)	11.6	3.8	2.4 - 5.1	6.1	7.7	6.4 - 9.0	4.4	4.2	2.9 - 5.4	1.6	3.0	1.6 - 4.4
Friability (in %)	4	2	1 - 4	3	2	1 - 4	9	11	7 - 19	28	37	23 - 61
Specific surface area (in m²/g)	1.0	1.0	0.8 - 1.2	1.0	1.0	0.9 - 1.2	3.3	3.3	3.1 - 3.4	0.2	0.4	0.3 - 0.6
Torque granulation barrel (in Nm)	4.2	3.6	2.5 - 5.3	4.3	4.7	3.4 - 6.5	1.9	1.9	1.4 - 2.7	1.5	1.6	1.1 - 2.2
Disintegration time (in sec)	31	62	-4 - 129	95	95	35 - 155	121	135	100 - 170	121	127	80 - 173
Tablet abrasion (in %)	0.7	0.9	0.6 - 1.2	0.7	0.6	0.4 - 0.7	0.2	0.3	0.2 - 0.4	*	0.7	0.5 - 1.1
Solid fraction @75N	0.76	0.80	0.77 - 0.82	0.79	0.80	0.78 - 0.82	0.80	0.81	0.79 - 0.83	*	0.86	0.84 - 0.87
Compression force @75N (in kN)	6.0	7.1	6.0 - 8.5	7.0	6.9	5.9 - 8.1	8.0	8.5	7.1 - 10.1	*	15.5	13.1 - 18.4
Ejection force @15kN (in N)	47	23	13 - 42	40	27	15 - 50	649	202	136 - 300	1138	338	216 - 528

In order to evaluate and verify the predictive quality of the models for data that were not included in the models, the difference between the predicted values (P) and the observed values (O) was calculated for each response for the 4 verification experiments using the following equation: $(O – P /O)*100$. The spider plot in Figure 12 provides an overview of the model verification assessment per response.
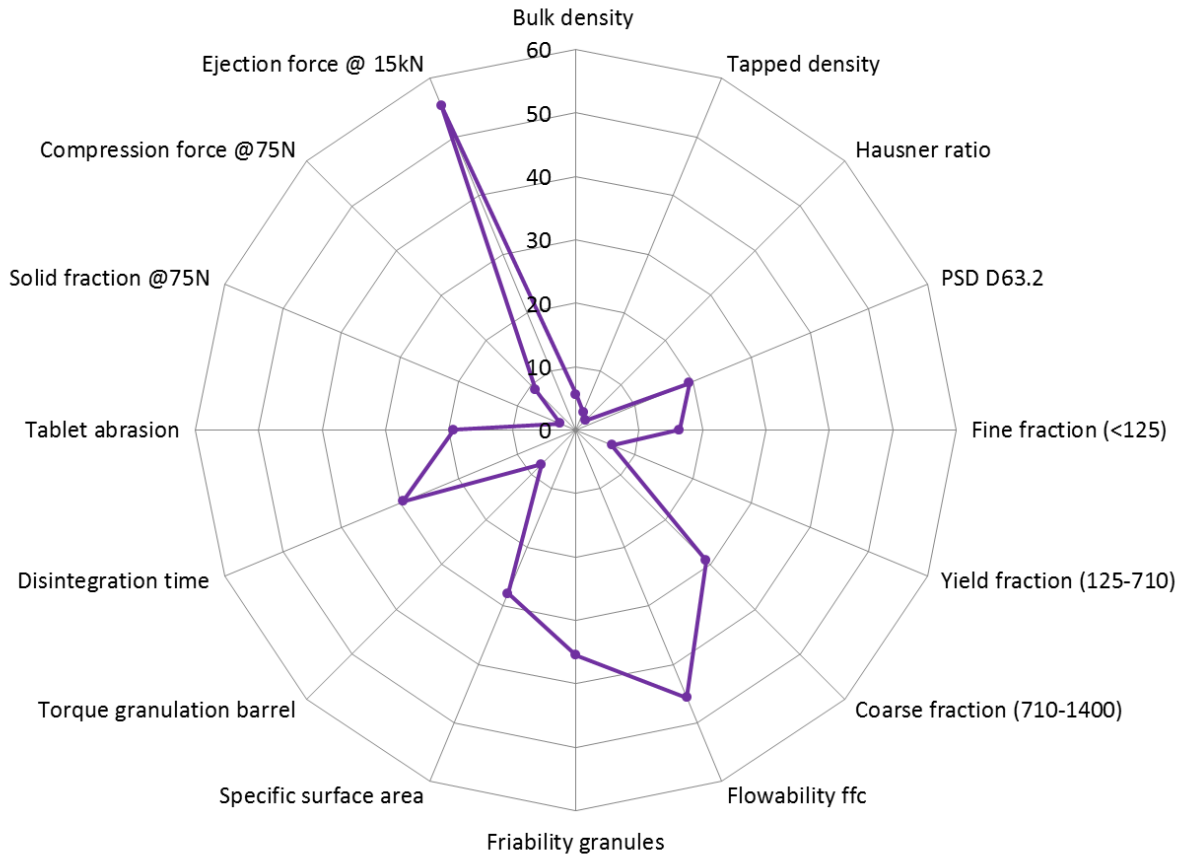

Figure 12. Spider plot: comparison of observed and predicted results per response. A higher percentage is indicative of a large deviation between observed and predicted values. The average deviation of the four verification runs is plotted.

The majority of the predictions were in alignment with expectations, indicating that high Q^2 model values resulted in a low P/O difference. There are some responses, however, where low Q^2 values resulted in limited differences between observed and predicted values (e.g. Hausner ratio, yield fraction or disintegration time), while the opposite was also observed (e.g. specific surface area or ejection force). A possible reason that predictions for the response ejection force resulted in a large P/O difference might be that parameters which distinctly influenced the ejection forces (such as concentration of lubricant in the formulation) were not included as factors in the experimental design and can thus not be explained by the model. Despite the limited variations in the response disintegration time (below 5 minutes for all samples) in combination with a low reproducibility of the centre points for this response, the P/O difference for this response was still acceptable. The low precision in the measurement method of granule

flowability might be responsible for the large P/O difference that was observed for flowability. With a low Q^2 value for the response flowability, the model indicated limited predictive power which was confirmed by a high P/O difference.

Despite these observations discussed above, the models provided good prediction results for granule and tablet responses and the external model verification confirmed the applicability of the existing model also for formulations which were not included in the statistical design, but composed of material included in the excipients PCA (see [12] for further details on the PCA).

4. Conclusion

By combining PCA with DoE, the number of design factors and subsequently the number of experimental batches was reduced while a broad experimental space of filler characteristics was investigated in the same statistical design. The application of statistical models enabled to link granule and tablet characteristics with the overarching properties using DoE and with the underlying excipients characteristics using PCA (Figure 13). Thus, a good understanding was generated regarding how formulation impact the quality attributes of granules and tablets. The formulation understanding presented in this research work, as well as the statistical models can be used to support a lean formulation development: for example, excipients with appropriate characteristics can be selected in order to compensate for unfavourable API properties and thus the number of required experimental runs can be reduced. Furthermore, the predictive power of the model can be used for formulation optimization and troubleshooting, by selecting fillers and binders with appropriate properties to improve suboptimal granule or tablet characteristics. The scope of this study is limited to binary placebo formulations consisting of one filler and one binder type. In order to understand potential non-linear effects of filler mixtures on drug product properties, further studies would be required which could follow a similar approach. Furthermore, an understanding of the impact of the API properties on the drug product pCQAs is also of interest. One approach would be to characterize the API according to the applied methods for fillers and update the PCA model by including the API properties. Based on the resulting three principle component values for the API, the statistical model should allow qualitative predictions of the API effect on the drug product pCQAs.
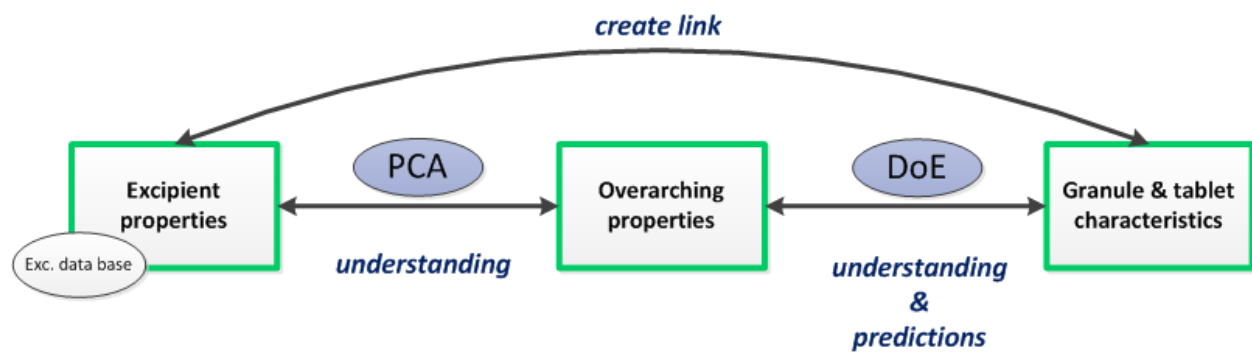

Figure 13. Combined PCA/DoE approach

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