Summary

The aim of pharmaceutical development is to design a high-quality formulation and manufacturing process that consistently delivers a drug product with the intended performance. Therefore, a systematic approach is required to obtain sufficient knowledge about the physical properties of the active pharmaceutical ingredient (API) and selected excipients and its effect on the final product critical quality attributes. Systematically logging the material properties using a multifaceted and standardized characterization protocol creates a multivariate database that can be utilized during drug product development. Establishing such a database can be the first step towards the identification of critical material attributes at each unit operation of a manufacturing process. The latter allows to limit time- and material-consuming characterization to a subset of informative techniques which suit the product and process of interest. Defining preferred API properties can even be used to steer the API crystallization and sizing process, whilst understanding the excipient properties will help to design a formulation more efficiently. As only a limited amount of API is available during drug product development, the main objective of creating an extensive material property database is to link the properties of materials with their performance and behaviour at each unit operation to establish predictive models and simulate the process and final drug product performance.

The background and general objectives of this thesis were outlined in **Chapter 1** and **Chapter 2,** with a focus on direct compression (DC) as the preferred route for tablet manufacturing. It was highlighted that development of robust tableting processes in a timely manner is still challenging due to incomplete mechanistic process understanding, fundamental understanding of the influence of raw material attributes, and limited usage of sophisticated process simulation tools.

Experimentally determining the effects of the involved process- and formulation parameters and thereafter optimization is labour-intensive, expensive and time-consuming. Therefore, investigating the possibility of raw material database management and process modelling using multivariate data analysis (MVA) techniques and numerical simulations of the compaction process based on finite element analysis (FEA) can provide a valuable and efficient addition to the current drug product development process.

In **Chapter 3**, a set of 55 powders covering excipients and APIs was characterized using over 20 techniques describing particle size and -shape, density, moisture content, powder flow, compressibility, aeration, surface area and triboelectric charging. Later (**Chapter 5**), multiple mechanical properties, including plastic, elastic, and brittle deformation, were determined based on in-die compaction tests. Principal component analysis (PCA) was then performed to elucidate correlations between the powders and their measured properties. PCA revealed (dis)similarities among materials based on their variation in overarching material properties. The model proved to be a useful tool to identify (anti-)correlated as well as non-relevant descriptors and/or characterization methods. The variability within all materials included in the raw material property dataset could be explained using a 4-principal component (PC) model. Cohesion, compressibility, flow, fluidization, particle size- and shape, permeability, porosity, powder rheology parameters, shear descriptors, specific surface area, true density and water uptake were identified as critical material attributes for this diverse group of materials. As applying MVA on a large dataset, including very diverse materials, is challenging, a methodology was presented to standardize model set-up and to improve the predictive ability of the PCA model.

Based on the raw material data analysis, formulation blends were selected in **Chapter 4,** containing different APIs and fillers covering a maximal area of the material variability space determined via the score scatter plots of the raw material PCA model. Disintegrant, glidant and lubricant concentrations were kept fixed in the selected blends. Formulation blend bulk properties were characterized with a minimum number of relevant tests, as derived from the PCA model of the raw materials. These characterization methods (ring shear test, compressibility, bulk/tapped density, helium pycnometry, loss on drying and aeration) were identified based on

the descriptors with a maximal positive or negative effect on each PC of the raw material PCA. This selection of relevant characterization methods was validated and proved to be sufficiently accurate in identifying (dis)similarities between materials. Further, this approach was extended for use towards blend characterization.

When constructing the PCA model after blend characterization, the PCs were similar to the raw material model. The variability between the blends could be explained by a 3 PC model where flow properties, blend powder density and moisture content were the overarching properties. Using this approach, the model can detect about 70% of the total possible variation between different powders compared to the full characterization of the raw material dataset. This methodology allows to limit the amount of material that is consumed for powder characterization and can save time by not performing non-relevant testing methods.

In **Chapter 5**, the before-mentioned blends were compacted on a compaction simulator, emulating a rotary production press, under different process conditions using a design of experiments approach. The raw material properties and blending ratios were then correlated with the process settings and resulting tablet quality attributes by fitting a T-shaped partial least squares (TPLS) model. This approach contributes to a better understanding of the DC process. Based on this platform, it is possible to determine which formulation and process parameters affect a tablet's quality attributes in a DC process. This predictive tableting platform (PreTaP) can guide the development process for new APIs by predicting an optimal formulation and finetune the compaction process settings based on a minimal number of relevant raw material characterization techniques and compaction tests. The PreTaP model provides thus a unique method to assess all the above-mentioned parameters at once. A case study demonstrated that an optimal formulation and suitable process settings could be identified with reasonable accuracy, which does not exclude the need for a development study but can be a useful tool to speed up this type of work.

The aim of **Chapter 6** was to evaluate the applicability of FEA simulations towards accurately predicting the compaction behaviour of pharmaceutical powders/blends and possible tablet defects. FEA was used to predict stress and relative density distributions inside tablets, which

were compared to distributions obtained from high-resolution X-Ray computed tomography (XRμCT) scans, where a novel way of image analysis was able to visualize the porosity distribution. For raw materials with different compaction behaviour, the simulations were qualitatively comparable to the XRμCT scans with only subtle observed differences. Possible explanations for the slight differences between the observations and simulations could be linked to the friction difference between the experiments and simulations, "time effect" (e.g., relaxation) between the production of the tablets and XRμCT scans and the cone-beam artifact in the XRμCT data. Nevertheless, the experimental observations/scans were in good accordance with the FEA simulations. This was further illustrated by a good quantitative prediction of the total tablet porosity for 1 blend at 3 different solid fractions. FEA simulations were used to predict visual tablet quality for 3 pharmaceutical relevant blends/processes. The simulations were able to predict high stress and stress relief areas, i.e., areas where potential tablet defects can occur, which translated into the relative density distribution. Visualizing the compaction behaviour allowed predicting good compaction behaviour as well as possible tablet defects such as capping and chipping.

Chapter 7 shows the applicability of this research in a broader international context from economic and social point-of-view, and how this research can contribute to future development programs.

Overall, this thesis contributes to a better understanding of the impact of powder properties and process settings on formulations, processes and final properties of the direct compaction-produced tablets. Applying this knowledge can reduce the consumption of expensive API during the product development phase. This PreTaP platform, which combines the use of MVA and FEA models, can be implemented for future development of formulations for DC and finding optimal process settings in a minimal amount of time.