Multivariate Synergies in Pharmaceutical Roll Compaction
The quality influence of raw materials and process parameters by design of experiments

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Akademisk avhandling

som med vederbörligt tillstånd av Rektor vid Umeå universitet för avläggande av filosofie doktorsexamen framläggs till offentligt försvår i KB3A9, KBC-huset, fredagen den 12 December, kl. 10:00.
Avhandlingen kommer att försvaras på engelska.

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Roll compaction is a continuous process commonly used in the pharmaceutical industry for dry granulation of moisture and heat sensitive powder blends. It is intended to increase bulk density and improve flowability. Roll compaction is a complex process that depends on many factors, such as feed powder properties, processing conditions and system layout. Some of the variability in the process remains unexplained. Accordingly, modeling tools are needed to understand the properties and the interrelations between raw materials, process parameters and the quality of the product. It is important to look at the whole manufacturing chain from raw materials to tablet properties.

The main objective of this thesis was to investigate the impact of raw materials, process parameters and system design variations on the quality of intermediate and final roll compaction products, as well as their interrelations. In order to do so, we have conducted a series of systematic experimental studies and utilized chemometric tools, such as design of experiments, latent variable models (i.e. PCA, OPLS and O2PLS) as well as mechanistic models based on the rolling theory of granular solids developed by Johanson (1965).

More specifically, we have developed a modeling approach to elucidate the influence of different brittle filler qualities of mannitol and dicalcium phosphate and their physical properties (i.e. flowability, particle size and compactability) on intermediate and final product quality. This approach allows the possibility of introducing new fillers without additional experiments, provided that they are within the previously mapped design space. Additionally, this approach is generic and could be extended beyond fillers. Furthermore, in contrast to many other materials, the results revealed that some qualities of the investigated fillers demonstrated improved compactability following roll compaction.

In one study, we identified the design space for a roll compaction process using a risk-based approach. The influence of process parameters (i.e. roll force, roll speed, roll gap and milling screen size) on different ribbon, granule and tablet properties was evaluated. In another study, we demonstrated the significant added value of the combination of near-infrared chemical imaging, texture analysis and multivariate methods in the quality assessment of the intermediate and final roll compaction products. Finally, we have also studied the roll compaction of an intermediate drug load formulation at different scales and using roll compactors with different feed screw mechanisms (i.e. horizontal and vertical). The horizontal feed screw roll compactor was also equipped with an instrumented roll technology allowing the measurement of normal stress on ribbon. Ribbon porosity was primarily found to be a function of normal stress, exhibiting a quadratic relationship. A similar quadratic relationship was also observed between roll force and ribbon porosity of the vertically fed roll compactor. A combination of design of experiments, latent variable and mechanistic models led to a better understanding of the critical process parameters and showed that scale up/transfer between equipment is feasible.

Keywords
Roll compaction, dry granulation, mannitol, dicalcium phosphate, design of experiments, orthogonal projections to latent structures, critical quality attributes, tablet manufacturing, quality by design, design space, near-infrared chemical imaging, texture analysis, modeling, scale up, instrumented roll, Johanson model.