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Promotionsverfahren von **Herrn Apotheker Stefan Klinken**
Auslage der Dissertation und Gutachten sowie Termin der mündlichen Prüfung
Anlage: Einseitige Zusammenfassung der Dissertation

Sehr geehrte Damen und Herren,

in dem oben genannten Promotionsverfahren wird die Annahme der Dissertation

Advanced Computational Methods for Time Series Analysis of Pharmaceutical Continuous Bulk Solid Feeding and Tableting

von den Berichterstattenden Prof. Dr. J. Breitkreutz und Prof. Dr. Dr. h.c. P. Kleinebudde beantragt. Sie kann zusammen mit den Gutachten in der Zeit

vom 26.04.2024 bis 07.05.2024

eingesehen werden. Bitte wenden Sie sich zur Einsicht an das Promotionsbüro (promotionmnf@hhu.de).

Einsprüche gegen diese Dissertation können nur zwei Tage nach der vorgenannten Frist geltend gemacht werden. Erfolgt kein Einspruch, so gilt die Dissertation als angenommen (§ 7 Ziffer (5) PO).

Sofern die Dissertation angenommen wird, findet die mündliche Prüfung am

13.05.2024 um 10:30 Uhr

im **Hörsaal 6 H** statt. Als Prüferinnen bzw. Prüfer sind vorgesehen:
Juniorprof. Dr. M. Hacker, Prof. Dr. N. Teusch und Prof. Dr. Dr. h.c. H. Stark.

Die Öffentlichkeit ist bei der Befragung zugelassen.

Mit freundlichen Grüßen
im Auftrag

Silke Krispin

Advanced Computational Methods
for Time Series Analysis of Pharmaceutical Continuous Bulk Solid Feeding and Tableting
Summary

Stefan Klinken

The advent of new technologies and trends in the development and manufacturing of pharmaceutical dosage forms has led to increased availability of data to describe the processes and properties of produced goods. Values from individual measurements do not only provide relevant information about processes, but the correlation of values within and between data series also contributes to the overall information contained in the data. The applicated methodology generally falls under the term of time series analysis.

In this current work the focus was laid on the subprocesses in the direct compression of bulk solids into tablets. Beside the compression process the powder dosing of the bulk solid materials was investigated. In this context a novel method for the qualification of powder dosing units was developed. The mathematical procedure utilizes permutations of the time series and Fourier transformations for the calculation of a measure of the entropy of the time series. The new procedure allows for the systematic analysis of deviations in stationary time series of the feed rate over time. The determination between chaotic events and systematic deviation from running mean of the time series was done based on permutations and subsequent transformation in frequency domain of the data. During this procedure artefacts within commonly used data were shown and discussed.

In the context of the compression step of materials in direct compression a database was created. It was analyzed regarding various features including measures of the compressibility, tabletability and compactability of the materials, as well as changes of these properties in mixtures of excipients. In two separated studies the diversity and reliability of the database was demonstrated. In the first investigation about pure pharmaceutical excipients different compression speeds, geometries of the tooling and target tablet masses were analyzed. It was shown that the accuracy of the compression speed of the compaction simulator was heterogeneous over the analyzed range. It was concluded that the punch speed of 3 mm s^{-1} seemed to be most applicable. Therefore, in the future expansions of the database this punch speed was targeted. The multivariate approach revealed that the tensile strength of tablets seemed to be correlated with certain shape of the compression profiles of the substances. Mainly the ab parameter in the Kawakita equation was found to highly correlate with the hardness of the produced tablets. The prediction of the tensile strength of tablets based on their compression profiles was therefore set as the target of this project. As the evaluation of pure components is of academic interest but of less practical impact an expansion of data to binary mixtures was done. The inclusion of ternary and quaternary systems in following studies further increased the diversity of the database towards settings comparable to industrial application. In the context of database management, the development of algorithmic data handling approaches was the key challenge in all these projects.
The final study presented in this work finalized the application of time series analysis in data of processes, related to direct compression. Based on the tools in natural language processing a LSTM layer based neural network was designed to analyze the curve shape of the compression profiles in the database. After a detailed descripted training procedure, the model was used to calculate the tensile strength of more than 800 tablets of various composition with a coefficient of determination 0.954. The detailed evaluation of residuals revealed no systematic correlation of errors in the model's prediction and properties of the materials investigated. The power of the model was demonstrated in the development of a procedure to calculate the tabletability profile of substances or mixtures based on a single compression process. Hereby an iterative curve stripping procedure was utilized for the generation of sub curves of the single compression profile. The applicability of the method was shown on 12 of the pure materials.
This thesis demonstrated the application of methodology of the field of statistics and data science in the evaluation of data of pharmaceutical processes in the production of tablets. The highlight of this work certainly is the material independent prediction of the tensile strength of tablets based on in process data. This method provides the first tool described in the literature to investigate the tabletability and compactability of materials solely based on inline data from the tableting process.