SYNTEGON
PROCESSING & PACKAGING

Fully Automated and DoE-Based Development of an Oral Solid Dosage Form

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Introduction

The cost of research and development in the pharmaceutical industry has risen sharply in recent decades, partly due to high statutory safety and quality requirements. Quality by Design (QbD) is a systematic approach to pharmaceutical development that emphasizes product and process understanding and process control, based on sound science and quality risk management. The QbD approach should enhance product manufacturability. Identifying potential critical quality attributes (CQAs) of the drug product, so that those product characteristics having an impact on product quality can be studied and controlled. It is also important to recognize that quality cannot be tested into products; it should be built in by design.

Intelligent automation offers the opportunity to improve both aspects of the drug development process. The goal of this work is to demonstrate the potential of a completely automated pharmaceutical development of a dosage form from powder to granules to finished tablet.

Objective

The aim of this study is to demonstrate the potential of fully automated and DoE-based development of oral solid dosage forms (tablets). The combination of design-of-experiments and automated execution of the individual process steps offers a new potential to accelerate the development process and to integrate more Quality-by-Design in the discovery and development of new drugs.

- Planning of all trials using Design-of-Experiments
- Automated execution of all experiments and analysis of the results

Material and Methods

For the preparation of the granules, different mixtures of Lactochem fine (DFE Pharma), Pharmacel 101 (DFE Pharma), micronized Paracetamol (APC 154, Atabay) and a 25% w/w solution of Kollidon® 30 (BASF) was used.

The Xelum R&D device for the continuous production of oral solid dosage (OSD) from Syntegon was used for the automated execution of the granulation experiments.

The tablet compression has been executed on a 25 stations rotary tablet press (TPR200, Syntegon, Germany), equipped only with 5 punches.

For the analysis, an automated tablet inspection system (CU-120, Pharma Technology, Belgium) was used. It combines a multipoint near-Infrared spatially resolved spectroscopic probe (NIR-SRS probe) to predict APIs concentration, a 3D microwave resonant sensor allowing to measure individual tablet weight, and a laser scanner to provide individual tablet thickness. Tests of physical attributes of the tablets based on conventional analysis methods were performed on an integrated 4-P tester (weight, thickness, hardness, and diameter).

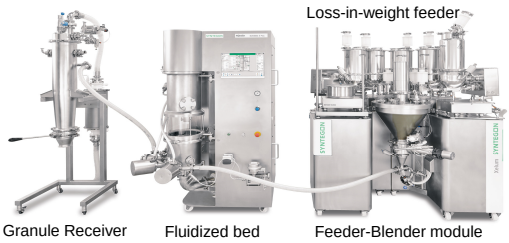

Fig 1. Xelum R&D closed process system blending and granulation

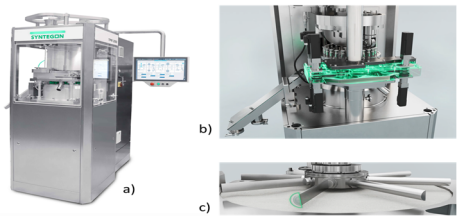

Fig 2. Automated Process Development at Tableting Machine
a) TPR 200 b) change 2-/3-paddle c) change round/rectangular blade

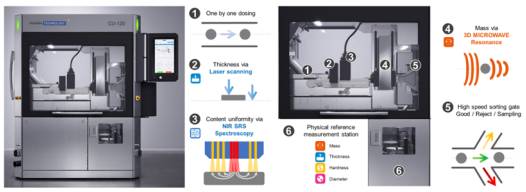

Fig 3. CU-120 Tablet Testing (Pharma Technology)

Results

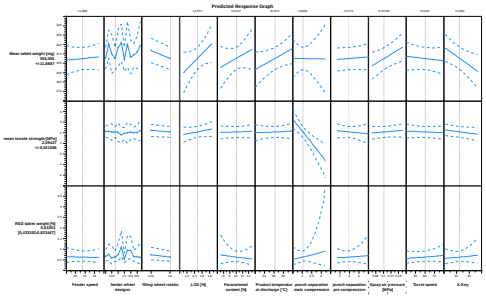

Fig 4. Predicted Response Graph for mean tablet weight, mean tensile strength and RSD of tablet weight

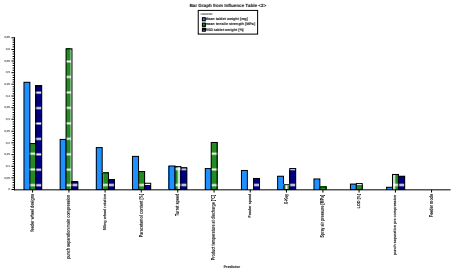

Fig 5. Influence/Impact factors on mean tablet weight, mean tensile strength and RSD of tablet weight

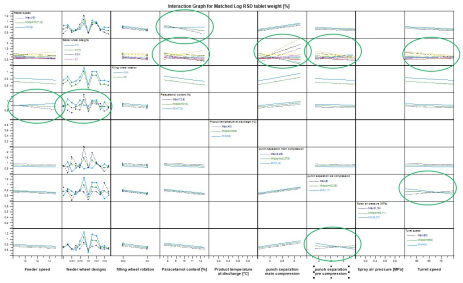

Fig 6. Interaction of the process parameters

26 different granule lots were prepared automatically , each with 5 kg, in two days. The API-content was varied from 7.5% over 10% to 12,5% of micronized paracetamol; the ratio of Lactose and MCC was kept constant. Different particle sizes of granules were achieved by variation of the spray air pressure (droplet size). By changing the drying time or the discharge end point (32°, 36° and 40°C), different moisture content of the granules was obtained.

265 tablet sample sets were automated prepared, each with 400 -600 tablets in two days. An automated feeder change between 2- and 3-paddle-feeder with round/cuboid blades, clockwise and counterclockwise rotation was used. Tablets were manufactured with 8 and 15 rpm feeder speed, 40 and 80 rpm turret speeds and different main/pre-compression forces. In figure 4, the statistical analysis and the predicted influence of the different process parameters on the product quality is shown. Especially the feeder design has a large impact on the RSD of the tablet weight, which is one the main important quality attribute and product manufacturability. In figure 5 the different impact factor on the product quality and in figure 6 the interaction between process parameter are described. By combined development and analysis of the formulation, the granulation process with the compression tests, several interactions of the manufacturing process and process parameters are identified.

More than 90,000 tablets out of 265 different tablet sample sets (received out of 26 X-keys) were analyzed in two days. Content Uniformity (NIR), weight (Microwave) and dimensions of the tablet were measured. The results by the CU-120 showed a good correlation with standard WHT- und UV/VIS-analysis. One further advantage in using the CU-120 is the non-destroying measurement.

Conclusions

Based on the automation of all development steps (granulation, compression and quality analysis) a high throughput and short development time was achieved. Based on 26 formulations, more than 260 tablets lots were prepared, each of them more than 400 tablets samples. All tablets were tested on a new tablet analysis tool, measuring weight, dimension and API content.

By the combination of DoE and automation it's possible to screen a larger parameter space, identify interaction of parameters and optimize the quality of the tablets (Quality-by-design). Because of the automation, the required amount of material is less than for a manual testing and intermediate change of the different modules like 2- and 3-paddle-feeder. Additionally, development times can be reduced by more than half through the applied automation.

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