Local Model Networks for the Optimization of a Tablet Production Process*

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Abstract. The calibration of a tablet press machine requires comprehensive experiments and is therefore expensive and time-consuming. In order to optimize the process parameters of a tablet press machine on the basis of measured data this paper presents a new approach that works with the application of local model networks. Goal of the model-based optimization was the improvement of the quality of produced tablets, i.e. the reduction of capping occurence and the variation of the tablet mass as well as the variation of the crushing strength. Modeling and optimization of the tablet process parameters show that it is possible to find process settings for the tabletting of non-preprocessed powder such that a sufficient quality of the tablets can be achieved.

1 Introduction

The pharmeceutical industry is increasingly aware of the advantages of implementing a quality-by-design (QbD) principle, including process analytical technology (PAT), in drug development and manufacturing [1], [2], [3]. Although the implementation of QbD into the product development and manufacturing inevitably requires large resources, both human and financial, large-scale production can be established in a more cost-effective manner and with improved efficiency and product quality.

Tablets are the most common pharmaceutical dosage form prepared by compression of a dry mixture of powders consisting of active ingredient and excipients into solid compacts. The process of tabletting consists of three stages: a) The powder mixture is filled into the die; b) compaction, where the powder is compressed inside a die by two punches, resulting in plastic and elastic

* This work was supported by the German Research Foundation (DFG), grant NE 656/3–1.

H. Deng et al. (Eds.): AICI 2009, LNAI 5855, pp. 241–250, 2009.

deformation and/or particles fragmentation, and c) ejection, where the tablet is ejected from the die and elastic recovery of the tablet may occur. An intensive elastic recovery can lead to separating the upper part of a tablet from the tablet body (capping). The mechanical behavior of powders during tabletting and the quality of tablets depend on the powder characteristics (formulation) and the tabletting parameters on the tablet press machine [4], [5], [6], [7]. In order to assure a high and repeatable quality of products the processes and formulations should be optimized. This is particularly important on high capacity rotary tablet presses which can produce a few hundred thousand tablets per hour and are very sensitive to product and process variables. A special challenge is the large scale production of products in form of tablets where the active drug loading is high ($> 50\%$ of the total mass of a tablet). Active drugs as organic molecules very often have inappropriate physical properties which prevent using direct compression of powder mixtures, which is the most economical production method (shortest process time, minimum cleaning and validation need, low energy consumption, environmentally friendly). The problem of capping is often observed in production of tablets with high drug loading. This problem can be solved either by formulation or process optimization. To find the optimal set of the parameters (main compression force, precompression force, compression speed ...) on the tablet press, it is possible to make a few tablets for each set of parameters, and then the operator can decide which settings should work best, and then starts the production. Fine machine setup optimization must be performed, due to some batch to batch variations of raw materials or some other variables. During the setup procedure, many of the tablets do not pass the quality control and must hence be discarded, which can be very expensive, regarding the price of the raw material and the number of trials, needed to find optimal settings. To optimize the quality of tablets and to reduce the number of faulty tablets, modeling and simulation procedures can be used, where a model of quality parameters with respect to process parameters must be developed. The raw materials used in tests should cover all the expected characteristics of raw materials that can be expected to appear in production. With the model, optimal settings of the machine can be found with respect to raw material characteristics, without further loss of raw material. The aim of the present study was the optimization of the tabletting process in order to diminish capping occurrence and the variation of tablet mass and crushing strength. Optimization was performed for the product where 70% of the tablet weight represent active ingredients, on the high capacity rotary-tablet press, in the standard production environment. Local model networks were used to model the relation between quality and process parameters.

2 Production of Model Tablets

Due to the high drug content and chosen manufacturing procedure (direct compression) changes in raw material characteristics can result in variable crushing strength of tablets, large tablet mass variation and most problematic, intense