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Short communication

Resolving tableting challenges and optimization of the tablet compression step of an immediate-release analgesic formulation

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Introduction

The purpose of development of the manufacturing process is to design a robust process that consistently results in a drug product with desirable critical quality attributes (CQAs) set at the beginning of product development.

The tablet compression is a critical step of the process that can significantly affect the disintegration and dissolution, and thus the bioavailability of the drug product. In the case of generic drugs, it also affects the bioequivalence to the reference drug product. In the case of an immediate-release analgesic formulation, the goal is to achieve a fast disintegration and dissolution of the drug product in order to achieve rapid pain relief.

The aim of this study was to optimize the tablet compression process of an immediate-release analgesic formulation and to resolve the tableting challenges that appeared during the process development.

According to the quality by design (QbD) approach, an initial risk assessment was performed to assess the critical process parameters (CPPs) and their influence on the product CQAs. In this case, the main compression force and the tableting speed were assessed as CPPs with the most significant influence on the product CQAs.

Materials and methods

The development of the formulation was done according to the QbD approach, using a wet granulation process. At the earlier stages of development, two sets of experiments were performed in order to resolve the capping and tablet sticking issues that appeared during tableting. In the first experiment designed to resolve the capping issue, two laboratory scale batches of the formulation were produced, with similar qualitative and quantitative composition, differing only in the level of:

- binder (9.07% and 10.90% respectively),
- glidant (0.87% and 1.00% respectively) and
- lubricant used (1.46% and 1.50% respectively), and in
- the pre-compression force applied during tableting (0.8 kN and 3.0 kN respectively).

In the second experiment, which was designed to resolve the sticking issue, two qualitatively and quantitatively identical laboratory scale batches were produced, differing only in the end point of the drying of the granulate, with one batch being dried until achieving an LOD of approximately 2.0-2.5% and the other to an LOD of max. 1.4%. Both batches were then tableted under the same conditions.

In order to optimize the tablet compression step and to assess the influence of the main compression force and tableting speed on the CQAs of the tablets, a full factorial experimental design with two factors on two levels, with three central points was performed. Said experimental design was created and analyzed with the software Modde Go. Seven optimization experiments in total were performed as well as an additional power failure simulation experiment. The two factors (independent variables) had the following levels: the main compression force low level was 20 kN and the high level was 35 kN (with a central point of 27.5 kN); and the tableting speed low level was 4800 tbl/h and the high level was 9600 tbl/h (with a central point of 7200 tbl/h). The average mass and uniformity of mass, hardness, friability, disintegration time and dissolution profiles were evaluated as dependent variables (responses) in the experiments.

All the optimization experiments were performed on a laboratory scale batch compressed on a laboratory rotary tablet press Korsch XL 100.

The power failure experiment was performed by stopping the tablet press temporarily to simulate a power interruption, and then restarting it. The goal of the experiment was to evaluate whether the process is robust enough to allow the previously set process parameters and product properties to remain unaffected.

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Results and discussion

Capping and sticking are common tableting problems that can occur due to a combination of formulation and process-related factors. Literature shows the main reason for capping and lamination is air entrapment between layers of the tablet during compression. Other causes are shear stresses when the tablet goes out of the die and tensile stress. Most commonly proposed solutions for this problem are using a higher pre-compression force and a lower main compression force, slower speed of production, optimizing the lubricant and binder level, and using a tapered die. The results of our first experiment show that the lab trial containing higher amounts of binder, glidant and lubricant, and tableted using a higher pre-compression force, under the same tableting speed (9600 tbl/h) is able to achieve the target tablet weight and hardness by using a lower main compression force (27 kN and 19 kN respectively) and the tablets do not show any signs of capping, while the lab trial with lower amounts of the said excipients and a lower pre-compression force produced tablets that show capping when produced at the same speed. These results corroborate the literature findings stated above regarding the resolving of the lamination and capping issue using a higher pre-compression force and optimizing the binder and lubricant concentrations. Tablet sticking is also a problem caused by many factors like the nature of the APIs; formulation, process and tooling-related factors. One way to resolve this issue is to make sure the drying of the granulate is adequate and doesn't result in excess moisture in the granules. The results of our second experiment corroborate these literature findings, showing that the lab trial that was dried until achieving an LOD of max. 1.4%, didn't show any signs of sticking, while the lab trial dried until achieving an LOD of 2.0-2.5% showed signs of sticking when compressed using the same process parameters. Regarding the results of the DoE optimization experiments, the goal was to investigate the influence of the tested factors as CPPs and to find their optimal ranges that will result in tablets that comply with the desired acceptance criteria. The relationship between the independent variables and the responses was established using partial least squares fitting. The models were assessed for adequacy with the summary of fit data. For the responses: hardness, friability, disintegration and dissolution, all indicators had values that indicate a significant model, whereas for the response average mass, the indicators show a non-significant model, since the average mass is not significantly influenced by the tested factors. The compression force was found to have a significant positive effect on tablet hardness and disintegration time, and a significant negative effect on the dissolution rate. Additionally, the compression force has a negative effect on the friability of the tablets, however the effect is not significant. The tableting speed was found to have a negative effect on tablet friability and hardness, but the effect is not significant. The tableting speed did not have a significant effect on the disintegration time and dissolution rate. An interaction between the two factors was found only regarding the response disintegration, with a significant negative effect on the response. The sweet-spot plot showed that tablet compression performed with a compression force within 20-32.6 kN and tableting speed within 4800-9600 tbl/h produces tablets with all responses within the desired acceptable limits. Main compression of 35 kN also produces satisfactory tablets, albeit with a slight decrease in the dissolution rate. Regarding the power failure simulation experiment, the results showed that all process parameters were well within the acceptable limits after the power interruption, and the produced tablets satisfy all acceptance criteria.

Conclusion

The capping and sticking issues have successfully been resolved with the aforementioned experiments. The results of the DoE, along with the power failure simulation, show that the compression process within the tested ranges of the tableting speed and compression force is robust and well optimized and consistently results in tablets that satisfy the acceptance criteria for the CQAs.

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