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Short communication

Design of Experiments (DoE) based determination of critical production variables in the manufacturing process of fixed-dose combination (FDC) drug containing Paracetamol

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Introduction

Quality by design (QbD) is a concept of designing and building quality into products during the manufacturing stage. In order to build quality, determination of the significant factors influencing product quality is fundamental. Over the last years, the concept of Design of Experiments (DoE) has been widely used to understand the effects of multidimensional interactions of input factors on the output responses of pharmaceutical products (Isa et al.,2018). When DoE is applied to the formulation or process development, input variables include the attributes (e.g., particle size) of raw materials and process parameters (e.g., press speed), while outputs are the critical quality attributes of the drug product. DoE also allows us to quantify the interaction terms of the variables and can help us to identify optimal manufacturing conditions (Lawrence et al., 2014). In order to optimize a process and improve product quality, it is critical to detect and understand the effects of the formulation and process variables on the tablet properties (Huolong et al., 2017). The aim of this study is to present the approach of using DoE method to determine the factors that could potentially influence the tablet hardness, uniformity of mass, and friability. It is anticipated that this information will be valuable for future selection of the grade of active substance or tableting process variables during the product lifecycle.

Materials and methods

Materials

The current study was conducted using a fixed-dose combination (FDC) drug containing Paracetamol. For the purpose of analysis of qualitative factor (Paracetamol grade), two different grades of Paracetamol were selected; grade A containing up to 40% fines and grade B containing 15% fines. Therefore, two blends containing different Paracetamol grades were produced. As excipients Microcrystalline cellulose (MCC-Avicel® PH102) Calcium hydrogen phosphate dihydrate (Dicafos D 160), Colloidal anhydrous silica (CAS-Aerosil®200), Sodium starch glycolate (Primojel), Croscarmellose sodium (CS-AcDiSol®), Glyceryl behenate (Compritol 888 ATO), Sodium lauryl sulphate (Kolliphor SLS fine) and Magnesium stearate (MS) were used.

Methods

Dry mixing technology using Lödige ploughshare® 10L laboratory mixer was used to prepare the final blends. Following the blending process, the rotary tablet press (Korsch Pro XL100) was used for the production of tablets.

The tablets were characterized for mass and uniformity of mass; using Sartorius Secura 224-1 CEU, friability using Erweka TAR 100; and hardness on Erweka Hardness Tester 425 TD.

Four parameters, three quantitative and one qualitative, were selected as the main variables for the

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tableting process. The first parameter was turret speed, for which a limit of 20 – 40rpm was set. The next two factors - main compression and pre-compression force were within the range of 10kN to 18kN and 0.5kN to 2kN, respectively. As a categorical variable – the grade of Paracetamol was evaluated.

Using the Design-Expert software (Version-7, State-ease Inc.) a 2^4 full factorial design with four center points was created in order to estimate the significance of the aforementioned input parameters and their interactions on output responses, the properties of the tablets (uniformity of mass, hardness, and friability).

Results and discussion

Statistical and Diagnostic Analysis of the Models

Uniformity of mass - The ANOVA analysis indicates significant model predictions (p value <0.0001; F-value of 24.71; PRESS=18.91 and $R^2 = 0.9277$).

The results reveal that the grade of Paracetamol had a significant impact on the uniformity of mass of the produced tablets (p value <0.0001) in a negative direction, as indicated by the negative sign of the regression coefficient (-0.89). In conclusion, using the grade A of Paracetamol, where the fraction of fines is larger, results in decreased uniformity of mass of the produced tablets.

"Turret speed" plays the next most critical role (p value = 0.0012). The positive sign of the regression coefficient (+0.54) indicates the increased value (decreased uniformity of produced tablets) when turret speed increased. At higher tableting speeds, the die filling time is shorter, resulting in increased weight variability.

The interaction effect between turret speed and Paracetamol grade significantly impacted (p = 0.0137) the uniformity of mass of the produced tablets in a negative direction (coefficient estimate = -0.37).

However, the grade of Paracetamol had the most significant impact on the parameter uniformity of mass, as evidenced by the magnitudes of the sum of squares (12.77 for the grade of Paracetamol, 4.60 for turret speed, and 2.23 for their interaction).

Hardness - The regression analysis of the obtained data proved the validity of the factorial model. The significance of the model was confirmed by the high F-value of 39.83 and a low p-value (< 0.0001) with a correlation coefficient (R2) of 0.9415, and PRESS=79.08, thus assuring a good fit model.

The results of the regression analysis reveal that the main compression force had a most significant impact on the hardness of tablets (p < 0.0001) in a positive direction according to the positive sign of the regression coefficient (+2.04). Main compression force has a direct impact on tablet forming thus on the hardness value. As expected, the hardness of tablets increases with the increase of the main compression force.

The grade of Paracetamol is an additional significant factor (p = 0.005) influencing hardness. The positive sign of the regression coefficient (+0.82) shows in particular that using Paracetamol grade B with less fraction of fines generates tablets with increased hardness.

No significant interaction among the variables was observed.

Friability - The regression analysis of the obtained data proved the validity of the factorial model for testing tablet friability, with an F-value of 24.71, a p-value < 0.0001, and a correlation coefficient (R^2) of 0.9565.

The magnitudes of the effect estimates show that the "grade of Paracetamol" is by far the most important factor influencing the friability of the tablets (p < 0.0001).

The friability is also dependent on the turret speed (p = 0.0033), and the interaction between the turret speed, pre-compression, and main compression force (p = 0.0007).

Conclusion

In this study, the influence of process variables such as the main compression and pre-compression force, the turret speed, and the grade of Paracetamol was investigated using a two-level full factorial design (2^4). The grade of Paracetamol was detected as the most significant factor affecting all process responses (tablet hardness, uniformity of mass, and friability).

The formulation will be further optimized based on the conclusion of the present study, using the coarser Paracetamol grade B.

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