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Short communication

Impact of qualitative formulation variables on critical quality attributes of tablets with fast disintegration

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Introduction

While problems with the quality of the drug product often arise from unfavourable properties of the API, it is well-known that the properties of the formulation excipients along with the manufacturing process can also have a marking effect on the quality of the product (Joneja et al., 1999; Paul and Sun, 2018).

In order to improve the quality of the product and the technological properties of the formulation, formulation changes were introduced in an existing high-dose drug product which exhibited fast disintegration but had history of problems with incomplete dissolution, higher friability and sticking on tablet press.

During the early stage of the development of the improved formulation, a screening of the criticality of qualitative formulation variables was performed and the effect was evaluated on the critical quality attributes (CQAs) of the drug product. The evaluation of the formulation changes involved use of a different binder type (povidone K25 and starch pregelatinized), filler (lactose monohydrate and microcrystalline cellulose) and lubricant (magnesium stearate and stearic acid). To enable fast disintegration, super-disintegrant sodium starch glycolate was used in all trials.

Experimental design 2^3 as a statistical QbD tool was used for examining the criticality of the formulation variables and their interactions.

Materials and methods

Batch size of each experimental run was 1kg. Quantitatively the formulation in all trials consisted of API - 83.3% w/w. Binders were added in quantity of 2.8% w/w for povidone K25 and 5.0% for starch pregelatinized. Lubricants magnesium stearate and stearic acid were added in quantity of 0.5% w/w. Super-disintegrant sodium starch glycolate was added in quantity of 2.5%. The fillers lactose monohydrate and microcrystalline cellulose were added in the remaining quantity to 100.0%.

Due to the high dosage of API in the formulation along with its micronized grade, the chosen manufacturing process was fluid-bed wet granulation. Fluid-bed granulation was performed in apparatus Mycrolab. API was mixed with binder, filler and disintegrant and granulated with water purified until an endpoint LOD of max. 2.0% was reached. Dried and screened granules were mixed with the extra-granular excipients: filler, glidant and disintegrant in a high-shear mixer Diosna P 1/6. The lubricant was added to the blend in the final stage in the high-shear mixer Diosna P 1/6. Each of the trials were then compressed on a Korsch XL 100 Pro rotary tablet press.

Evaluation of raw data and model interpretation was performed using MODDE Go® statistical software. In order to predict the variability of the results for response variables with varying the values for independent variables, Multiple linear regression (MLR) was used.

Disintegration time was tested on apparatus for disintegration Erweka ZT322 on 6 tablets. The target criteria for disintegration are less than 2 minutes.

Hardness was tested on a hardness tester Erweka TBH 425TD. Friability was tested on friability tester Erweka Friability Tester TAR 120. The acceptance criteria for hardness are 9-18 kP and for friability max 1%.

Dissolution was performed on apparatus 2 – paddle (PhEur) in 900ml medium of 0.1M HCl, speed 75 rpm, and after the process of dissolving the results were determined

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by using complexometric titration. The acceptance criteria for dissolution are NLT 70% in 30 minutes.

Results and discussion

2^3 full factorial design with three factors at two qualitative levels and three replicates was applied. The three varying factors were: binder, filler and lubricant type. Regarding the experimental design, the following factors and levels were tested. Factor X_1-binder, with levels: povidone K25 and starch pregelatinized, factor X_2-filler, with levels lactose monohydrate and microcrystalline cellulose, and factor X_3-lubricant with levels magnesium stearate and stearic acid. The effects were evaluated on CQAs hardness, disintegration time, friability and dissolution of API.

The statistical parameters for evaluation of the quality of the model were calculated and showed that the model is significant and valid, fits the data for all responses and has high predictive ability. The skewness test for disintegration required log transformation of the response for improvement of the predictive ability of the model.

Highest significant effects on hardness of tablets were observed for the binder type and filler type. Povidone K 25 resulted in a larger increase in hardness of tablets than pregelatinized Starch. Microcrystalline cellulose resulted in a larger increase in hardness than lactose monohydrate.

Significant interaction was observed among the binder and the filler influencing the hardness of tablets. This means that the effects of the binder on the hardness depend on the filler type used. Tablet hardness increased at a faster rate with a change in binder from starch pregelatinized to povidone K25 when lactose monohydrate is present as filler instead of microcrystalline cellulose.

The highest significant effects for disintegration time were observed for the filler type, binder type and lubricant type. Faster disintegration can be expected with the choice of binder Starch pregelatinized, filler microcrystalline cellulose and lubricant stearic acid. Accordingly, the trial with povidone K25 as binder, lactose monohydrate as filler and magnesium stearate as lubricant showed a prolonged disintegration of 2.2 min compared to the other trials with fast disintegration times of less than 1 min.

The highest significant effects for the friability of tablets were observed for the binder type and lubricant type with Starch pregelatinized resulting with a higher increase in friability compared to povidone K 25 as binder, and magnesium stearate resulting with a higher friability than stearic acid. The trial with Starch pregelatinized as binder, lactose monohydrate as filler and magnesium stearate as lubricant showed unacceptable friability of 2.3%. The other trials with starch pregelatinized as binder had borderline to high friability of 1% - 1.6%.

The dissolution was significantly affected by the choice of lubricant: stearic acid and magnesium stearate. A significant decrease in dissolution was observed in the trials with magnesium stearate with some results out of the acceptance criteria of NLT 70% in 30 minutes. The negative effect of magnesium stearate on dissolution has been widely discussed (Wang, Wen and Desai, 2010). As both magnesium stearate and stearic acid are hydrophobic in nature, the faster dissolution of tablets with stearic acid could be due to the differences in the mechanism of lubrication, the effectiveness of stearic acid at higher concentrations compared to magnesium stearate, or a solid-state incompatibility with the API.

The dissolution was unaffected by the other formulation factors as independent factors or their interactions.

After reviewing the results, the trials with complete dissolution, lowest disintegration time, optimum hardness, and friability were selected for further study.

Conclusion

From the results of our study it can be observed that qualitative changes in the formulation in terms of use of different excipients with the same function in the formulation could have a significant effect on the CQAs of the drug product. In the current formulation the choice of lubricant was significant for the dissolution properties of the formulation, while the choice of binder and the binder-filler interaction was important for the disintegration, hardness and friability of the tablets. The chosen 2^3 full factorial design with qualitative levels was a beneficial tool for evaluation of the criticality of the excipients as factors and their interactions on the CQAs of the tablets during the early stage of development of the improved formulation.

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