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Short communication

Influence of the drug particle morphology on physical characteristics of granules prepared with wet granulation technology process

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Introduction

The purpose of this short paper is to present the influence of the different particle morphology of a nonsteroidal anti-inflammatory active pharmaceutical ingredient (API), incorporated in high dose content (85.5 w/w %) immediate release formulation, on the physical characteristics of granules obtained with wet granulation technology process.

In case of highly dose immediate release formulations, the physical characteristics of the API such as: particle size and shape and particle size distribution have the main impact on quality attributes of the granulate including the flowability. In order to evaluate the effect, micronized APIs with similar particle size (d90<30μm), but different in the crystal morphology (API A1- needle shaped crystal and API A2-cutted needle shaped crystal) were used. The both APIs, due to their micronizied quality, have low flowability and compressibility characteristics. Because of this, it is essential to apply wet granulation technology process.

Granulation is the process of agglomeration of powder mixture, which results in the enlargement of the particles. This is often necessary for manufacturing of solid dosage forms such as tablets (Gokhale et al., 2005). The granulation process is particularly sensitive to variables such as different physical properties of solid particles (particle size distribution, 'wettability' and crystal shape of active substance and excipients) (Belohlav et al., 2007). The materials, which are compressed into tablets, must possess adequate flowability, density and compressibility (Gokhale et al., 2005). It is well known that spherical particles flow better (Chan and Heng, 2005) compared with irregular morphology of particles.

Materials and Methods

Materials

API (A1 and A2) was supplied from two different manufacturers, Copovidone (Kollidon VA 64) was supplied from BASF, Ludwigshaften, Germany, Crosscarmellose sodium (Ac-Di-Sol) was supplied from DuPont, Cork, Ireland, Talc was supplied from Merck, Darmstadt, Germany and Magnesium sterate was supplied from FACI S.p.A., Carasco, Italy.

Methods

Two formulations (G1 and G2) with the same qualitative and quantitative composition were prepared with wet granulation process using high shear mixer granulator. The only variable was drug particle morphology. Water, purified was used as a granulation aid in the wet granulation process. Different shape and particle size distribution are the key parameters for determining the optimum amount of granulation aid (Belohlav et al., 2007). During producing the final blend, all the process parameters were constant.

Microscopy technique (Malvern-Morphology G3S) was applied to confirm the different morphology of the

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API. Physical characteristics such as bulk and tapped density, flow and particle size distribution of API and final blend were evaluated by Tapped Volumetar SVM 102, Erweka and Retch AS200 Control. Additionally, Carr index and Hausner ratio were calculated to characterize the flow properties of the two crystals morphology of API themselves and their incorporation in the final blend.

Results and discussion

Different particle morphologies, A1-needle shaped crystal and A2-cutted needle shaped crystal, were confirmed by optical microscopic photography. According to the obtained results for bulk and tapped density for the A1 (0.201g/mL, 0.254 g/mL) and A2 (0.181g/mL, 0.235g/mL), A1 has greater density from A2. Both of them have specified passable flowability characteristics based on calculated Carr index (A1-21%, A2-23%) and Hausner ratio (A1-1.27, A2-1.30).

Wet granulation process was performed using A1 for obtaining granulate-G1 with quantity of granulation aid which comprised 18.8% of the quantity of the dry powder mixture. Adding the same quantity of the granulation aid for obtaining granulate with A2, produced overwetted granulate. Therefore, the optimized quantity of the granulation aid was 14.6% of the dry powder mixture with API A2 and proposed excipients (granulate-G2). The different particle morphology can be considered as a reason of this behavior. Furthermore, the dried granulate G1 was screened on a bigger sieve size compared to G2. When the same sieve size was used as G2, the screened granulate contained large quantity of fines, which compromised the flowability. On the other hand, when bigger sieve size was used for granulate with A1, gave tablets prone to lamination. The greater granule strength of G2 and fragile granules of G1 can explain this fact. G2 (0.584g/mL, 0.663g/mL) had higher bulk and tapped density than G1 (0.503g/mL, 0.572g/mL). In addition, G2 and G1 have higher bulk and tapped density than the initial density of A1 and A2, which confirmed the granulation theory. The calculated values of Carr index (12%) and Hausner ratio (1.14) were the same for the both granulates which shows very good and similar compressibility. The improved flowability was confirmed by the results for flow rate and with their respective standard deviation of G1 (6.2s/100g, SD=0.50) and G2 (5.5s/100g, SD=0.64), so content uniformity problems were further not expected.

Conclusion

Particle morphology of the active substance strongly affects the physical characteristics of granulates prepared with wet granulation technology. Even if the same process parameters and the same qualitative and quantitative content of excipients were used, slight modifications in the manufacturing process had to be made due to the presented different properties of both APIs.

Adjustment of the quantity of the granulation aid and appropriate selection of the sieve sizes for the dry granulates, resulted with robust process capable of producing final product with similar characteristics and CQAs according to defined criteria with both APIs.

References

Belohlav, Z., Brenková, L., Hanika, J., Durdil, P., Rapek, P. and Tomasek, V., 2007. Effect of Drug Active Substance Particles on Wet Granulation Process. Chem. Eng. Res. Des. 85(7), 974-980. https://doi.org/10.1205/cherd06205

Chan, L.W. and Heng, P.W.S., 2005. Drug substance and excipient characterization, in Parikh. D.M. (Eds), Handbook of pharmaceutical granulation technology, second edition, Synthon Pharmaceuticals Inc., U.S.A., pp. 79-107.

Gokhale, R., Sun, Y. and Shukla, A.J., 2005. High-shear granulation in Parikh. D.M. (Eds), Handbook of pharmaceutical granulation technology, second edition, Synthon Pharmaceuticals Inc., U.S.A., pp. 191-228.