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Short communication

Approaches for optimization of formulation and manufacturing process of low-dose tablets

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Introduction

Developing formulations for low load drugs where small amount of the active pharmaceutical ingredient (API) is blended with a large amount of excipients is challenging (Alyami et al., 2017). For a low-dose formulation, drug substance is usually micronized to achieve acceptable blending homogeneity and content uniformity. Micronized drug with a small particle size could be static, cohesive, adhesive, and fluffy with low density (Zheng, 2009).

Another challenge for this particular formulation is the degradation of the used active substance in the presence of moisture. Therefore, besides achieving good content uniformity, approaches for optimization of formulation using different methods of stabilization were taken into consideration along with the selection of the most suitable manufacturing process.

Direct compression (DC) is a simpler tablet manufacturing method and an attractive platform for manufacturing tablet drug products. However, developing a low-dose drug product using direct compression poses great challenges to consistently producing high product quality. Major challenges include control of the physical properties of drug substance, mixing homogeneity, segregation, and lubricity.

On the contrary, during the granulation process, small fine or coarse particles are converted into large agglomerates called granules. Wet granulation technique produces a mixture of API and excipients that has acceptable flow, compressibility, and compactibility for tableting. However, wet granulation/fluid bed drying method of tablet manufacture is multistep process, and thus is time-consuming, complex, and expensive (Shanmugam, 2015).

The purpose of the study was optimization of a formulation and manufacturing process by which the low dose API will be uniformly mixed in a tablet as a final drug product while attaining stabilization of the active substance.

Materials and methods

Formulations

During the formulation development, few experimental laboratory trials produced with direct compression contained different fillers such as: low moisture silicified microcrystalline cellulose, lactose monohydrate, mannitol or low moisture microcrystalline cellulose. The formulation of choice produced with direct compression (formulation A) contains: low moisture microcrystalline cellulose, low moisture partially pregelatinized maize starch, hydrated silicon dioxide, glycine hydrochloride and glycerol dibehenate.

The experimental laboratory trials produced with wet granulation/ fluid bed drying were manufactured using ethanol, combination water/ ethanol or only water. The binder used is hydroxypropyl methyl cellulose (HPMC). Other excipients contained in the formulation of choice produced with wet granulation (formulation B) were lactose monohydrate, microcrystalline cellulose, partially pregelatinized maize starch, croscarmellose sodium and sodium stearyl fumarate.

Production processes

Experimental laboratory trials prepared with direct compression were mixed in Diosna P 1/6 high-shear mixer granulator. The laboratory trials prepared with high-shear wet granulation and fluidized-bed drying process were

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mixed in Diosna P 1/6 high-shear mixer granulator during the binder addition and wet-massing phases. Fluid bed drying was carried in Huttlin MycroLab drier. The final blend was mixed in a low shear mixer Erweka AR403. The final blends were compressed on a Korsch XL100 laboratory scale rotary tablet press machine equipped with standard concave punches.

Testing methods

Flow properties of the final blends were evaluated according to Ph. Eur. 10.7 (2.9.36). The tablets were characterized for: mass; hardness, diameter and thickness, friability (Ph. Eur. 10.7 (2.9.7)); and disintegration (Ph. Eur. 10.7 (2.9.1)). Tests for dissolution, content uniformity and related and degradation products were performed using in-house HPLC methods.

Results and discussion

The optimization of formulation and manufacturing process were directed by the dose of 1.21% of the active substance, its properties and taking into consideration the susceptibility to degradation under moisture.

The final blends for both formulations (A and B) have similar flow properties assessed as good and suitable for further processing. Characterization of the physical properties of the tablets of both formulations showed that all obtained results for tablet mass, diameter (6.0 ± 0.3 mm), thickness (3.0 – 3.5 mm), hardness (5-10 kP), friability (less than 1.0%) and disintegration (max. 15 min.) are within the respective predetermined acceptance criteria. The results from the average assay (99.7% and 99.6% respectively for formulation A and formulation B) and content uniformity (5.6% for formulation A and 4.7% for formulation B) indicate that the homogeneity was achieved with both formulations and manufacturing processes applied. Fast release of the active substance (>85% in 15 minutes) and similar dissolution profiles with the reference product in 0.1M HCl as the medium of choice was seen in both cases.

The initial values for total impurities are 0.10% for formulation A and 0.03% for formulation B which are within the predetermined acceptance criteria of max. 1.0%.

Of particular concern in direct compression process is the loss of API from adherence to or absorption onto metal surfaces. The purpose in optimization of the formulation and the process of direct compression was to improve formulation and process that would minimize adherence of API onto metal surfaces, to minimize the segregation potential by selection of excipients with appropriate particle size distribution, as well as to optimize the mixing regime. Low moisture excipients used in direct compression formulations showed significant improvement in terms of stabilization of the active substance. The best results were achieved by addition of desiccant to control trace amounts of moisture and moisture transfer from the surrounding environment such as hydrated silicon dioxide, and acid donor such as glycine hydrochloride.

Surprisingly, despite the sensitivity to moisture of the active substance, better results regarding wet granulation process were achieved in the formulations where only water was used as a granulation liquid rather than ethanol or their combination. HPMC present in the formulation manufactured by wet granulation showed promising results in terms of protection against moisture by reducing the contact of the API with the rest of the excipients. The short duration of the process enables minimum exposure time of the active substance to water.

Conclusion

Different approaches can be used in formulation and process development and many challenges regarding low dose drugs can be overcome by selection of the right combination of excipients in the formulation as well as the manufacturing process.

The formulations of choice that showed satisfactory homogeneity and preferred physico-chemical properties would be further evaluated on screening stability studies.

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