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Short communication

Influence of pre-blend holding time on critical quality attributes of film-coated tablets

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Introduction

The particle properties of the API has a significant impact on the bulk characteristics of the pre-blend in which it is incorporated, which is critical for its behavior in the further production phases and obtaining a final product with the desired quality that meets its predetermined acceptance criteria (Wang et al., 2022). Namely, micronized particles are often used to improve the content uniformity in the mixture, to enhance solubility and subsequently dissolution performance and bioavailability. But this fact is valid only when micronized API exist as primary particles with larger specific surface area available to greater penetration of the media, not when they unintentionally clump together in agglomerates that leads to low surface area and lower exposure to the media. (Villers, 1996). Essentially, particle size reduction may cause cluster size enlargement and agglomeration strength due to increased surface energy, which could impact partitioning of API and reduce the dissolution rate (Saravanan et al., 2020).

During optimization phase of low dose product (film-coated tablets with 5 % w/w of API), it was determined that hold time of 24 hours of the intermediate product pre-blend for roller compaction leads to decrease in the dissolution rate of film coated tablets compared to the case when the mixture is compacted into ribbons immediately after mixture prepartion. Since the API particles incorporated in the mixture are in free state for a longer time, probability to adhere to each together under Van-der Waals Forces and electrostatic charges is higher, taking into account that the influence of roller compaction forces that will lead to their unifrom arragement into ribbons that are further granulated to uniform spherical particle, occures in the next production step.

Materials and methods

Pre-blend for roller compaction as intermediate product includes micronized active substance with poor aqueous solubility, freely soluble in anhydrous ethanol provided by Honour Lab limited, lactose anhydrous and silicified microcrystalline cellulose as fillers, silica colloidal anhydrous as glidant, crosspovidone as disintegrant and magnesium stearate as lubricant.

Manufacturing procedure is standard for producing immediate release film-coated tablets, using dry granulation technology. In the first phase, the API is mixed in a triturate with a part of filler lactose anhydrous and part of the glidant Silica, colloidal anhydrous in a plough shear mixer (Lödige 10L, Germany). The triturate was passed through a suitable screen size to de-lump any agglomerates

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(Conical screen mill Quadro Comil U5). Further, the sieved triturate has been blended with rest of fille lactose anhydrous, disintegrant- crosspovidone and filler silicified microcrystalline cellulose and lubricated with part of magnesium stearate in a same plough shear mixer. The obtained pre-blend has been compacted into ribbons which are subsequently milled to form granules (AlexanderWerk WP 150). Then, granulate has been blended extra-granularly with the rest of magnesium stearate into final blend. The final blend is compressed on a rotary tableting machine fitted with punches and dies of the required shape and size (Korsch XL 100, DE) into tablet cores and then film coated with the previously prepared film coating suspension Opadry TF 273F220004 yellow (O'Hara Labcoat, Canada).

Three laboratory trials of film-coated tablets in scale size of 3 kg were prepared with differenet holding times of the pre-blend for roller cmpaction process.

The duration of pre-blend holding time before roller compaction was up to 24h and 12h in laboratory trial 1 and 2 (LT1 and LT2), respectively. The pre-blend of laboratory trial 3 (LT3) was immediately roller compacted.

The film-coated tablets were analyzed for *assay* and *dissolution rate of API.*

In vitro drug release studies were performed for 15, 30 and 45 minutes ± 2 % in 900 ml buffer pH 6.8 simulated intenstinal fluid (Ph.Eur) as dissoluiton media maintained at 37 ± 0.5 ˚C. The test is performed on 6 tablets.

HPLC method was used for determining the assay and dissolution rate of API in drug product. The content of dissolved API was calculated from the API peak area ratio in the chromatograms of the sample and the standard solution at detection wavelength of 224 nm.

Results and discussion

The Quality target product profile (QTTP) was set according to reference drug characteristics (round, biconvex film-coated tablets with mass of 260.00 mg ± 7.5% and diameter 9.00 mm). Obtained results from the *in vitro* release studies indicate that the duration of pre-blend for roller compaction has an impact on assay and the release behavior of the API from final product.

Evaluated results of LT1 showed significant differences to the assay and released rate of API compared to the LT2 and LT3. The average value for assay is 86.8%; 98.1% and 98.3%, respectively. The average value for dissolution is 77.1%; 93.8% and 91.8% in 15 minutes, 82.0%; 95.6% and 95.8% in 30 minutes and 83.7%, 96.3% and 97.3% in 45 minutes, respectively for LT1, LT2 and LT3.

The assay and dissolution rate of API in LT2 and LT3 is higher compared to LT1, indicating that pre-blend holding time longer than 12h adversely affects critical quality attributes of final product as a result of spontaneous agglomeration.

Conclusion

Based on the evaluated results, it can be concluded that prolonged pre-blend holding time (>12h) leads to decrease in assay values and dissolution rate of API from immediate release film-coated tablets as final product. Thus, prior to next production phases, pre-blend is recommended to be compacted immediately or with a maximum holding time of up to 12 hours after its preparation.

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