Macedonian pharmaceutical bulletin, 68 (Suppl 1) 221 - 222 (2022)
Online ISSN 1857 - 8969
*DOI:*10.33320/maced.pharm.bull.2022.68.03.105
Short communication

Improvement of content uniformity in low-dose powder blends: critical formulation and process variables

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Introduction

The safety and efficacy of solid oral drug products, as well as their robust performance, are ensured by meeting the specified values of critical quality attributes (CQAs). Blend homogeneity and content uniformity in drug products are CQAs of primary importance, especially for direct compression (Crouter, Briens, 2019; Jakubowska, Ciepluch, 2021; Zheng, 2008). Drug product development and manufacturing should align with Quality by Design (QbD) principles, where critical material attributes (CMAs) and critical process parameters (CPPs) are taken into consideration in regards to their impact on product CQAs (Fukuda et al., 2018; ICH Q8 (R2), 2017; Roy, 2012). According to the Product Quality Research Institute (PQRI) Blend Uniformity Working Group (BUWG) survey the blend-uniformity variation was always less than 10% for direct compression processes, used routinely to manufacture low-dosage solid forms (Hancock and Garcia-Munoz, 2013).

Formulation variables

Major CMAs for achieving a homogenous blend are: mean particle size, particle size distribution, particle shape, and blend flowability (Jakubowska \and Ciepluch, 2021; Zheng, 2008). The best content uniformity can be reached if the shape, size and density of mixed particles are as similar as possible, while the spherical shape is preferred (Muselík et al., 2014). Micronized, needle or flat particles require longer blending time due to aggregate formation, although these particles have less tendency to segregate (Zheng, 2008). Larger particles tend to be free-flowing and smaller particles tend to be cohesive due to inter particulate forces associated with the individual particles (Deveswaran et al., 2009). The process of blending, for cohesive powders relies not only on the properties of the cohesive particles but also on the adhesive interactions in a binary mixture (Alyami et al., 2017). The cohesiveness of a powder depends on the size of the particles that make up the powder: the smaller the particle, the higher the cohesion (Janssen et al., 2020). High drug loading capability of excipients is ideal in such formulations (Alyami et al., 2017). Excipients form the bulk of the dosage form and their functional properties are critical.

Although the lactose is the oldest direct compression filler-binder, it still remains one of the most widely used substances for this purpose. Spray-dried lactose is a good excipient for use in low-dose formulations. It is largely inert, inexpensive, safe and exhibits excellent flow characteristics due to its spherical particle shape and narrow particle size distribution (Janssen et al., 2020; Zheng, 2008).

A proper Design of Experiment (DoE) is an efficient way of defining the excipient levels and selecting the optimal formulation. After formulation optimization, the operator should perform additional studies to optimize the manufacturing process (Zheng, 2008).

Process Variables

Most important CPPs are the type of mixer (blender) and the design of the mixing system (e.g., geometry and blend mechanism, blender size, fill level, rotation speed, mixing duration, blender loading mode) (Zheng, 2008). The root causes of blend content uniformity problems are:

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suboptimal blending, thief sampling error, weight control, loss of component, segregation, insufficient particle distribution and analytical error (Deveswaran et al., 2009). If the mixing time is too short, the blend will not mix properly. If the mixing time is too long, "overmixing" can occur (Jakubowska and Ciepluch, 2021; Muselík et al., 2014). The longer the blending time, the greater the time of contact between all the particles. This may induce better homogeneity due to increased chances of collision of the particles (Alyami et al., 2017).

There is an increasing need for methods that provide accurate and reliable information about the mixture homogeneity. Process monitoring can be achieved by performing routine testing of the process samples using off-line, at-line, in-line and on-line instrumentations. Vibrational spectroscopy techniques (Near-Infrared spectroscopy and Raman Spectroscopy) are used as process analytical technology (PAT) tools to monitor the mixing process and mixing endpoint (Asachi et al., 2018; Crouter and Briens, 2019; Makraduli et al., 2020; Šašić, 2007).

Conclusion

When developing a low-dose tablet formulation, content uniformity of the active substance has to be achieved. Direct compression is one of the simplest methods of tablet production when the mechanical properties of the powder blend are primarily derived from the properties of the excipients. The content uniformity of the active substance also depends on the efficiency of the mixing process. It is of primary importance to optimize the mixing (blending) process, that is, to optimize the content uniformity of the active substance in the dry mixture from which the final tablets are produced. A proper DoE study and PAT tool have to be selected for establishing the best formulation and manufacturing process, as well as process and content uniformity monitoring.

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