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Short communication

Comparation between fluid bed granulation and high shear mixer as a techniques of choice for achieving optimum homogeneity for low dose solid pharmaceutical dosage form

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Introduction

Formulation and manufacture of low-dose tablets require careful production, because blending a large amount of bulk powder, such that each amount has a total active pharmaceutical ingredients (API) content within a few percent of the target concentration is a significant challenge. The British Pharmacopeia (BP) defined low-dose formulation as those formulations "containing less than 2 mg or 2% drug loading (w/w) of active pharmaceutical ingredients (API), and that's why content uniformity, among basic requirements for the manufacturing of solid dosage units, is a particularly important attribute for drug products containing low levels of API (Fayed et al.,2020; Siew, 2018).

While formulating a tablet with low-dose of API three factors can directly contribute to content uniformity problem: non uniform distribution of the drug substance throughout the powder mixture or granulation, segregation of the powder mixture or granulation during the various manufacturing processes, tablet weight variation. To overcome the problems of content uniformity and provide dosage units within the acceptance criteria, granulation is usually the first choice for preparation of homogeneous, segregation-resistant blends because of the strong API-excipient bonds formed by the agglomeration process (Kukkar et al., 2008; Mao et al., 2013).

Based on the literature data and progress in pharmaceutical research, apart from conventional formulation techniques (like wet granulation, dry granulation, and direct compression) various new techniques have been reported such as high shear granulation, fluidized bed spray granulation and spray drying (Mao et al., 2013).

The objective of the present study was to achieve optimum homogeneity for a low dose formulation (0.04 % w/w) by comparing the two types of closed granulating systems: fluid bed granulator and high-shear mixer.

Materials and methods

Materials

Active pharmaceutical ingredient (API): Cyanocobalamin 100 % (Hubei Hongyuan Pharmaceutical Technology Co., LTD), Premix Complex of B vitamins.

Excipients: Lactose Monohydrate 200 mesh (Granulac®200), Maltodextrin (Lycatyb DSH), Hydroxypropyl Cellulose, Maize Starch, Povidone (Kolidon® 30), Croscarmellose sodium (Vivasol®); Citric acid, monohydrate; Natrium Citrate, Sillica Colloidal anhydrous (Cab-o-sil®), Magnesium stearate and Talc pharma grade – (excipients were used in concentrations in accordance with recommended concentrations from Handbook of Pharmaceutical Excipients).

Method

Experimental batches were produced with different techniques: dry mixing and wet granulation (fluid bed granulation and high shear mixing). In wet granulation API was dissolved in aqua purificata:ethanol 96 % (50:50), and blended with excipients including a binder Povidone 30, and other excipients such as Citric acid, monohydrate and Natrium citrate in order to adjust the pH of the solution in which Cyanocobalamin is stable. In fluid bed

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granulation powders were agglomerated by spraying the solution from the top spray of the machine, while in high shear granulation the binding solution was gradually added through a funnel. Each batch was repeated three times, in order to see if the repeatability of the results would be obtained.

Uniformity of content

According to Ph. Eur 11th the term 'uniformity of dosage unit' is defined as the degree of uniformity in the amount of the active substance among dosage units and the uniformity of dosage units can be demonstrated by either of two methods: content uniformity or mass variation. Drug content was measured by an HPLC method (2.2.29) (Eur. Ph., 2022).

Results and discussion

The quality control of all experimental batches was performed with an aim to characterize the uniformity of drug content and based on the obtained results the proper technique process to be chosen. In each experimental batch the results for drug content were in the acceptable criteria, but the difference in content uniformity results was evident especially in experimental batches produces by dry mixing.

Table 1. Results obtained from analyzing content uniformity (%)

Experimental batch	Dry mixing	Fluid bed granulation	High shear mixing
1	18.5	1.4	10.9
2	26.6	2.0	7.7
3	19.1	1.4	13.4

In the table of results, we also present the results that we've obtained with dry mixing formulation technique which show us from the very beginning that it's not a technique process of choice and direct us that powder mixing is the critical step before tableting, which produces a uniform blend to be compressed into tablets.

In contrast to the results for content uniformity of dry mixing, result that we've achieved by using granulating techniques fluid bed granulation and high-shear mixer both are in acceptable criteria. However, despite that both techniques gave us acceptable results, in the table shown above we can see that better results are obtained with fluid bed granulation. The two techniques differ technically in the method of solid agitation. In the fluid bed granulation, the binding solution for granulation is sprayed over the powder, in a direction opposite to the air flow, and granule formation occurs by adhesion of the liquid droplets to the solid particles. Also, drying of the particles occurs simultaneously during the granulating process. Unlike fluid bed granulation in high shear mixing an impeller maintains the powder in agitation in a closed vessel. As binder solution is add gradually the liquid droplets are distributed on the dry mixture and the formation of granules begins. In this process, the power of the impeller is one of the critical steps because agitation forces are preventing the development of large agglomerates. Also, in high shear mixing the drying occurs after the mass is transferred in another piece of equipment (binder or fluid bed dryer). In the end when the wet mass from both granulation techniques was dried to the desired moisture, we also notice a small difference between the shape and density of granules that we've obtained. This difference between the granules shows us that maybe it's one of the main reasons for obtaining different results for content uniformity while using both techniques.

Conclusion

According to the obtained results, it might be seen that both granulation processes are of choice while formulating tablets with low-dose of API. Also, we come to conclusion that selection of the correct equipment and monitoring its critical parameters are one of the solutions of segregation problem in this type of formulations.

Despite the good initial results for both techniques, our technique of choice is fluid bed granulation because itis multi-operation equipment and minimizes transfer operations of powder blend. In order to prove the effectiveness of the method it is necessary to perform a scale - up and validation of the process and stability study should also be completed.

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