Ardena Insight

Powder blending in early-phase drug product development: Balancing art and science

Powder-filled capsules are arguably the most widely utilised dosage form in early-phase clinical studies. They can flexibly be manufactured in different dose strengths through variations of capsule fill volume, are easily administered and offer a straightforward way to blind the formulation and impart taste-masking properties. To enhance manufacturability of powder-filled capsules, either by hand or via high-speed capsule-filling machines, the active pharmaceutical ingredient (API) is usually formulated with excipients into a powder blend. Formulation as a blend is generally also envisaged to enhance quality and performance of the final capsule, e.g. in terms of content uniformity, chemical stability and disintegration. The present newsletter provides an overview of Ardena's approach to early-phase powder blend development.

The development of a suitable blend starts with the collection of preformulation data. The API characteristics that are typically assessed within Ardena at the start of a capsule development project are particle size distribution, particle morphology, loose and tapped bulk density, cohesivity, flowability and hygroscopicity. The information gathered from these measurements provide the formulator with a good basis to support excipient selection. However, prediction of powder behaviour is complex given the multitude of influencing factors and the complexity of their interplay. Powder blending in the early phases of development is therefore as much a science as an art, with formulators designing blends relying not only on exact experimental data but also on experience.

In general, one could say that the selection of excipients is driven by the desire to avoid segregation, which could lead to reduced processability and poor content uniformity. To minimise the risk of segregation, it is advisable to select excipients with similar physicochemical nature and particle size as the API. It is good practice to evaluate the chemical compatibility of the excipient with the API prior to inclusion in the blend. Excipients are preferably also available in a wide range of particle sizes, to enable selection of a grade with similar particle size as the API.

We generally recommend keeping the number of ingredients in the blend as low as technically possible, to reduce complexity and minimise the risk of segregation. Disintegrants are best avoided if not strictly needed, and lubricants should be used with caution as their inclusion may cause irreversible segregation and also hamper disintegration of the final dosage form.

After thoughtful selection of the excipients, the blending process development can start. We generally mix all excipients first (except for lubricants, which are always added at the very end of the blending process) and then incorporate the API. Proper excipient blending means that the bulk filler is thoroughly mixed with a (hydrophilic) glidant, such as colloidal silicon dioxide. The glidant covers the surface of the filler, correcting surface irregularities, reducing interparticle friction, decreasing surface charges, and hence improving the flowability of the blend. Proper mixing involves sieving and re-blending steps, the need of which is assessed on a case-by-case basis. To promote adequate homogenisation, it is also good practice to add the excipients in layer-wise fashion to the blender.

After preparation of the excipient blend, it's time to incorporate the API. Geometric dilution, a well-known principle in pharmaceutical space, also has its utility in early-phase clinical manufacturing.In practice, geometric dilution implies that the blending process starts by mixing equal portions of API and excipient blend. This small mass of blend (1:1 API:excipient ratio) is then further diluted in a stepwise manner until all excipient blend is consumed.

The type of blender, its fill volume and mixing time are also critical determinants of the blending process. V-blenders (also known as twin-shell tumbling blenders) are commonly used in the Ardena formulation labs and GMP cleanrooms. As the V-blender tumbles, the powder continuously splits and recombines, with mixing occurring as the material free-falls randomly inside the vessel. The fill volume is preferably kept between 30% and 70% of the shell volume. The blender speed should be selected carefully, and processing time gains obtained by faster blending should be balanced against potential losses in process efficiency. Higher blending speeds indeed provide more shear forces which is efficient for mixing, but also result in higher dust formation which increases the chance of segregation of the finest particles. And if blending speed increases above a critical threshold, process efficiency drops dramatically due to the centrifugal forces exceeding the gravitational forces.

In summary, careful excipient selection based on the API characteristics is key to obtaining a successful powder blend. The blend is preferably kept as simple as possible and only comprises ingredients of which the utility has been demonstrated. The order of ingredient addition during the blending process is important and is best performed while adhering to general principles such as layering and geometric dilution. The choice of the blending process parameters is key to achieving adequate homogenisation, whereby faster blending is not necessarily better.