Perfecting PSD for Tableting

Technical Article: The Impact of Granule Particle Size Distribution for Tablet Compression

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Overview

Granules formed by either wet or dry granulating processes must have an optimal particle size distribution for good granule flow, die filling and tablet integrity. Drug delivery formulators have other considerations as well.

The density of the milled granule that fills the tableting die must be such that the correct API dose is present in the pressed tablet. This is known as content uniformity. Meanwhile, the dissolution and consequential bioavailability of the active pharmaceutical ingredient impacted by the granule particle size distribution must be considered. Balancing these objectives can be somewhat of a challenge.

Besides particle size, other factors inherent to the granules contribute to the formation of a robust tablet. The selection of the correct binder such as polyvinylpyrrolidone, methacrylate-based binders and others affect the hardness and bond strength of the pressed tablet. In general, to prevent the formation of voids and while maintaining the desired hardness, a narrow particle size distribution of the granules is generally required. Excessive fines are to be avoided to prevent pressed tablet defects such as capping and lamination.

Images show tablet defects due to excessive fines in the sized granules

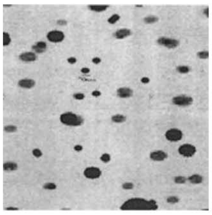
Photo example of lamination

Photo example of capping

However, some fines are needed to fill the interstitial spaces between the larger particles. The particle size distribution relating to tableting is often expressed as the weight distribution at the following percentiles: 90th (d_{90}), 50th or median (d_{50}) and 10th (d_{10}).

One critical parameter is the width of the particle size distribution. This is often measured as a ratio of d_{90} / d_{10}.

In general, a bell normal particle distribution is desired with a d_{90} at 800 to 900 microns. Two to three percent fines below 150 microns may also be desirable.



Brick and Mortar Analogy: The finer particles that reside between the larger particles act as a mortar whereas the coarser particles are the bricks. This is sometimes known as the particle packing factor.

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Functional Aspects of a Narrow Particle Size Distribution

Keeping fines to a minimum promotes good flow of the granules through the feeding system of the tablet press and into the die. Complete and uniform die filling are needed for consistent active pharmaceutical ingredient dosing and consistent gross tablet weight.

As mentioned, not only do excessive fines lead to tablet defects, but hamper flow and die filling. Moreover, excessive fines do not form adequate mechanical bonds that can lead to unacceptable tablet hardness. Finally, excessive fines can create undue dust developed during compression, leading to waste and reclamation concerns.

Mesh	Microns	% Retained
18	1000	3
18 - 20	850 - 1000	17
20 - 40	425 - 850	37
40 - 60	250 - 425	24
60 - 80	180 - 250	11
80 - 100	150 - 250	6
Pan		2

The left particle granulometry is typical of a milled granulation prior to compression.

This representation of a narrow particle size distribution has an approximate d_{90}/d_{10} ratio of 4.3.

In this example, the approximate values are: d_{90} 800μ, d_{50} 450μ and d_{10} 185μ.

Wet Granule Sizing

The dispersion of the granulated wet mass by means of a conical mill equipped with a large open area screen is of vital importance to proper granule formation. Non-dispersed wet mass dries unevenly and granules with wet centers can result. These larger granules take longer to dry and present issues for post drying size reduction. Larger granules reside in the post dryer conical screen mill for a longer period which can cause excessive fines in the milled granule to be compressed.

Above, a Hanningfield Uni-Mill is integrated to the discharge of a high shear granulator. The wet mass is uniformly dispersed in the mill. This facilitates drying and enhances final dry sizing. The suction fan equipped with the fluid bed dryer is employed to convey the wet mass from the granulator, through the conical mill and into the fluid bed dryer bowl.

Wet Processed Granule Characteristics

The hardness, density, friability, and particle size of the granule is a result of several factors:

> Type of binder(s), liquid and solid

> Particle size, density, and morphology of other excipient materials

> Method of drying: tray or fluid bed

> Loading of trays and fluid bed bowl

> Drying temperature and duration

> Particle size distribution consistency of excipient materials e.g. binders, diluents/bulking agents, and carrier agents

The Role of the Hanningfield Uni-Mill Conical Screen Mill for Dry Granule Sizing

For the size reduction of most dry granulations, a conical screen mill is an ideal choice for a typical d90 between 800 and 1200 microns. Typical conical screen mills operate at a low nominal impeller tip speed of approximately 14 m/s, excellent for controlled size reduction. The conical screen design has high total screen area avoiding excessive residence time. The stressing mechanism can be changed to adapt to the hardness and friability of the in-feed granules by means of a tooling change i.e. impeller type, screen type and sometimes the addition of a baffle.

For harder granules, it has been found that a tighter particle size is possible utilising a rasping screen with a round profile impeller. This is despite a 1mm aperture rasping screen having lower open area compared to a standard round opening screen. There is 25% open area for the standard round perforated screen versus 22% open area for the rasping screen. The rasping screen changes the fractal stress mechanism from primarily compressive forces to shear forces.

Above, a Hanningfield Uni-Vac system gently vacuum conveys the dried granules from the fluid bed dryer bowl and through the Uni-Mill conical screen mill. Product is received and discharged to a rigid intermediate bulk container. At this stage, lubricants can be added to the IBC and tumble blended in a method know as in-bin blending.

Fine tuning granule density to achieve the proper dosing when the size of the tablet press dies and punches are fixed, is often achievable. The goal is to shift the entire particle size distribution curve to the finer side, thus increasing density in some cases. Typically, this is accomplished solely with a change to a smaller screen peroration opening. Sometimes, slight speed changes are required to minimise fines.

Conical screen mills are available in a wide arrange of sizes. They scale up reliably with little variation in the particle size distribution. In the application of both wet mass milling (pre-drying) and post drying final sizing, conical mills integrate well with fluid bed dryers and high sheer granulators. They offer high containment potential as well. Lastly, the conical screen mill's simple design lends itself to rapid cleaning and deployment.

Conclusion

Perfecting particle size distribution for tableting is a balancing act. Good granulometry is impacted by selecting an upstream milling technology with a high degree of flexibility and accuracy.

Conical mills help achieve this balance. They possess the versatility for both wet milling (dispersing wet mass for improved drying) and dry milling (creating calibrated particle size post-drying) - in both cases, they can be easily integrated with high-shear granulators and fluid bed dryers. Meanwhile, simple speed and tooling changes help refine and shift particle size distribution as required.

Ultimately this helps to deliver an optimised bell curve; creating granules with good flow and fill characteristics and producing a tablet with robust form and apposite drug delivery (content uniformity and bioavailability).

Summary Points

Hausner Ratio

Predict granule flow by evaluating the tapped granule density ratio divided by the loose granule density; known has the Hausner ratio. A Hausner ratio of 1.0 to 1.2 indicates good flow and fill granule properties.

Drying Performance

Upstream wet mass granulation and dispersion has a significant effect on the post fluid bed drying size reduction, and fluid bed dryer performance.

Uni-Mill Tooling

Uni-Mill tooling can be optimised to align with the dispersion or dry milling process. Tooling can also be optimised for granule hardness, friability as well as desired particle size distribution.

Good Flow Characteristics

A primary objective of OSD tablet developers is to create granules with good flow characteristic so that uniform tablet press die filling is ensured.

PSD Bell Curve

A bell normal distribution with a small percentage of fines is required for a good particle packing factor that results in excellent pressed tablet integrity without defects.

Wet and Dry Milling

The Hanningfield Uni-Mill conical screen mill is ideal for wet mass dispersion prior to drying as well as post drying granule sizing prior to tableting.

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