

New trends in solid dosage forms production

The operation of a high speed tablet press has two main requirements on the feed material: it needs to flow well to assure a homogeneous filling of the dies; plus it needs to compress well. These requirements can be achieved in two different ways.

It is possible to use expensive raw materials with special physical characteristics allowing a direct compression of the mixture, but this method doesn't work for all formulations, especially if very high or very low drug content is required or if the API deforms during compression (mainly caused by plastic deformation). In some cases the application of a roller compaction step can improve the situation but it's unsuitable if the materials deform under pressure by brittle fracture. This method can also be expensive if large amounts of materials need to be produced.

The alternative is to use wet granulation. This requires a significant up-front investment however cheaper raw materials can then be used as they will be converted into the desired physical state by the process. Wet granulation has been around for decades but over recent years some exiting new developments have taken place that will be described in this article.

The use of a high shear granulator with a fluid bed dryer is still the most widely used combination. Its advantages are obvious: it combines the most productive and versatile granulator with the most effective dryer. For large volume products and long campaigns this gives unbeaten productivity. Downsides are the high upfront investment, the large space required plus the long downtime for product changeovers.

Recent alternatives addressing these issues are:



1. Integrated High Shear Granulation and Fluid Bed Drying Suite

Single Pot technology

A mixer/granulator that dries granules in the same equipment without discharging is commonly called a single pot. The granulation is done in a normal high shear processor; there are various options for drying in single pots. The traditional heat source comes from the heated dryer walls; the heat transfer is related to the surface area of the walls and the volume of product treated. This direct heating method is therefore only effective for small scale use.

Introducing stripping gas into the pot allows large scale operation. A small quantity of gas is introduced in the bottom of the equipment which then passes through the product bed, improving the heat flow from the wall into the product. The gas also improves the efficiency of vapour removal. However, as the heated wall is the only source of drying energy, linear scale-up is not possible. This problem is exacerbated if the material to be processed is heat sensitive (as this limits the wall temperature); if

water is used as a granulation liquid (it has a high boiling temperature under vacuum and a high heat of evaporation); and if used for larger-scale production the surface/volume ratio deteriorates as the volume increases.



2. Single-Pot R&D solid dosage suite

Microwave energy can be used to overcome these limitations. This provides a further source of energy and has the additional advantage, with organic solvents, that only pure organic vapours will be treated on the exhaust side, and not a mixture of solvent and large volumes of process gas, as would be required in most other wet granulation technologies.

Single pot technology offers various advantages depending on the product mix. The machine can be cleaned in less than 2 hours – even for substances that don't dissolve easily in water – so it's a highly productive tool for short campaigns that require a high number of product changeovers.

As a one pot operation it is perfectly suited for the handling of potent substances. By using appropriate technologies for loading, unloading and sampling - such as split butterfly valve systems - substances such as hormones or oncology products can be processed without the need for PPE (Personal Protection Equipment). Additionally, it offers very high yields as a result of the minimal surface area in contact with the product, a huge advantage when processing expensive products.

FlexStream™ - tangential spray system

Granulation can be performed using fluid beds fitted with spray nozzles. For many years the top spray position was preferred, but now the advantages of tangential spray systems have become obvious. The main advantage is the location of the spray nozzle, in an area with significantly higher shear forces that allows the processing of formulations that could previously only be granulated in high shear processors. Additionally the introduction of the new FlexStream™ range of fluid beds also eliminates the problem of scale up.

In recent years fluid beds have improved dramatically in response to competition from single pot technology. It is possible to have completely closed material handling by linking with upstream and downstream equipment. Also, fully automatic cleaning (CIP) in fluid beds using stainless steel filters has now reached a level that compares favourably with what is possible in a single pot.



3. FlexStream™ Fluid Bed Processor

Another advantage of the FlexStream™ range - recently introduced by GEA - is that for drying, granulation and coating only one product container is

required. Tests with more than 100 different products prove that the performance of the FlexStream™ processors are always at least equal, and in most cases superior, to conventional top spray granulators or Wurster coaters.

These advantages make it the most versatile and cost effective solution.

Continuous Tableting Line

As a result of various FDA initiatives there is a huge interest in continuous processing. In response to this, GEA introduced ConsiGma™ Continuous Tableting Line. A typical installation consists of continuous raw material feeding, a continuous granulator, a semi-continuous dryer, an evaluation unit, a blender for the addition of the outer phase and a tablet press. For raw material feeding there are three options: a pre-blend of all components can be used; up to four components can be fed individually; or a pre-blend of all excipients and the API can be fed independently. The last option is of particular interest if potent APIs are involved as the overall residence time in the system is less than 30 minutes.



4. Continuous Processing Technology Center

One main advantage of such a system is that it can, by adjustment of the process parameters, compensate for variations of the input parameters, for example different raw material properties, leading to an end product of consistent quality.

While the reduced footprint and the reduced need of operators makes it very attractive from an investment point of view, it offers many other advantages.

The only scale up parameter is time, which means scale up problems that are often seen with conventional batch equipment no longer exist, allowing research orientated companies to shrink their development times while generic companies can start their development programs later.

With the unit installed in the GEA test centre, a typical product changeover is done in less than six hours. This makes the technology not only attractive for large volume productions but also for a wider product mix. An additional advantage here is that there are no fixed batch sizes required allowing the production of flexible amounts as required by the market.

Finally the system offers a unique solution for effervescent production. As a result of the ultra short residence time the pre-effervescent reaction happens much less than with any other wet method.

Conclusion

Wet granulation is a very important technology in the process train of tablet production. Exciting developments over recent years have boosted the performance of the technology significantly allowing optimal solutions to be identified for product mix and production scenario.

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