Bigger is NOT Better – Sample Preparation in the Pharmaceutical Industry

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The trend is to have small samples having smaller and more controlled particle size and yet remain representative

In the analysis of solid material, the popular adage that 'bigger is better' certainly does not apply. The goal is to produce particles that are sufficiently small to satisfy the requirements of the analysis while ensuring that the final sample accurately represents the original material. The 'particles' of interest to the analyst generally range from 10µm to 2mm. Additionally there are many applications, where even finer sizes are needed. One example are active ingredients, where it is necessary to grind in the submicron range. Finally for DNA or RNA extraction mechanical cell lysis is well-established.

Materials differ widely in their composition and physical properties. Hence, there are many different grinding principles that can be applied, and this, together with other variables such as initial feed or 'lump' size, fineness needed and amount of sample available, results in a wide range of models available to the researcher. Some grinding processes may require aids that will help the size reduction process while at the same time, leave the material uncontaminated or unaltered in any way. The most common example of such an aid is that of cryogenic grinding where soft material (animal tissue/plastics) will not grind unless it is made brittle through the use of dry ice or liquid nitrogen. Finally, choosing the most appropriate mill will often require the help and support of the manufacturer. This process may include a trial test sample to help finalise the decision.

Figure 1. Retsch CryoMill

Smaller Particles, Finer Grinding

In the pharmaceutical industry the science and study of particles including their size and shape are very critical. Particle characteristics can affect many different areas including inhalation delivery systems, tablet dissolution characteristics, formulation quality and solubility or absorption. As in many industries, there is a move towards smaller particle sizes and therefore, there is an increasing need to grind finer and finer. The following sections address specific applications that are common to the pharmaceutical industry:

1. Animal/human tissue: In order to extract DNA and RNA from mammalian tissue, the material has to be homogenised or ground as part of the procedure. Since most animal tissue, and particularly lung, liver and muscle, is soft at room temperature and also susceptible to damage due to the heat naturally generated during the grinding process, it is necessary to chill the material in liquid nitrogen prior to or during grinding. Cryogenic mills or small mixer mills are ideal for this since the grinding vessel, complete with material and media, is either permanently cooled in LN_2 during grinding (for example, in the Retsch CryoMill, *Figure 1*) or can be completely immersed in liquid nitrogen prior to the process. The powerful grinding action will result in complete homogenisation before the sample has had a chance to warm up. This method also can be applied to some of the harder tissues, such as bone or cartilage, as well as plant material.

2. Active ingredients: Active ingredients in the sub-micron range can be achieved by planetary ball milling *(Figure 2)* where the material is processed in a jar using grinding media made of the same material as the jar. In a similar manner to the solar system, the mill rotates the jar on a turntable but at the same time, the jar rotates on its own axis in the opposite direction to the 'system' rotation. This generates very high milling energy resulting in fast reduction to very small sizes. Single micron and sub–micron sizes can be achieved through wet milling, usually in alcohol, and dry milling is used when the size reduction demands are not as high. Grinding jars are available in a number of different sizes and materials, the latter being necessary to avoid contamination from heavy metals, for example, during the grinding process. The smaller mixer mills mentioned above can also be used for size reduction of active ingredients and are particularly useful when small sample amounts are available or the material requires pre-chilling prior to grinding.

3. Finished Products: In the pharmaceutical industry, finished products often exist as tablets or capsules and these bring their own sets of challenges when it comes to grinding. Classical size-reduction techniques involve methods such as grinding the tablets in a mortar, which is both time consuming and labour intensive. Grinding mills can do the job in a fraction of the time, produce a much more consistent sample and free technicians for more productive tasks. The following techniques can be used for tablet grinding as well as other pharmaceutical applications:

- Mixer Mills are particularly suitable for the rapid and efficient grinding of tablets and capsules. Grinding takes approximately two minutes and the use of a closed jar guarantees loss-free grinding. The process is suitable for tablets of different sizes and hardness with a capacity up to 20mL of tablets.
- Knife Mills are the ideal choice for coated tablets since these will not be crushed in a mixer or ball mill due to the coating usually made of sugar or gelatin. With capacity over 100mL, such a mill is also suitable for grinding large tablets.
- Ultra-centrifugal mills have a wide range of applications. The unique grinding action makes it suitable for grinding medium to large tablets when strongly varying quantities (25mL – 5L) are required.
- Mortar Mill, the mechanised version of the classic hand pestle and mortar, is well suited for tablet grinding as well as mixing and homogenisation of powders, suspensions and pastes.

4. Other pharmaceutical applications: There are other applications that involve the production of "particles" used in pharmaceutical and medical applications. An interesting application is the grinding of human cortical bone to produce raw materials used in various preparations for use in bone grafts and implants. The bone material is often processed in tissue banks around the country and then reprocessed in the companies who produce the final products. The process usually requires two different mills, the first of which is a cutting mill. These heavy-duty mills are designed to reduce larger pieces of bone down to sizes of a few millimeters or less. Some of the material produced by this mill can be used without additional processing but the remainder is then processed in an Ultra Centrifugal Mill such as Retsch's ZM 200 *(Figure 3)*. This versatile mill will then further reduce the size of the bone pieces to the sizes needed for their intended use. The whole process is fast, efficient and has an excellent recovery rate. Both mills have designs that make cleaning easy and include many safety features to protect the users from possible injury.

Figure 2. Retsch Planetary Ball Mill PM 100

Figure 3. Retsch Ultra Centrifugal Mill ZM 200

Conclusions

The analytical world is getting smaller both figuratively and literally. The importance of the pharmaceutical industry in particle technology cannot be overstated and, directly and indirectly, it has been responsible for many of the advances that have occurred during the past few years.

In size reduction technology, there is a trend towards smaller samples that have a smaller and more controlled particle size and yet remain representative of the material being analysed. Companies must offer a selection of size reduction equipment and accessories that can meet these demands.