Why particles size is important in pharmaceutical industry? Is it really problematic?

In the pharmaceutical industry, particle size has become one of the key aspects in the development of the active pharmaceutical ingredients (APIs) and quality control of solid oral dosage forms.

As we know, the physicochemical and biopharmaceutical properties of biologically active substance can be highly affected by crystal size and its distribution (CSD), also called as particle size distribution (PSD). According to the latest scientific reports, it is estimated that almost 80% of new promising molecules having biological activity are rejected during the research and development process due to the low water solubility what is strongly related to the bioavailability and release of the drug. Therefore, the API solubility parameters especially ingredients belonging to class II and IV of the Biopharmaceutical Classification System can be improved by increasing the crystal surface – reducing the crystal size. The particle size significantly affects powder flowability, bulk density, hygroscopicity, compatibility, porosity and blend uniformity. These parameters influence every stage of tablet manufacturing (including compression, coating, granulation and mixing), which affects the effectiveness and shelf life of the drug. The particle size is not only important in the last stage of the tableting process. The PSD control is also relevant for the manufacturer of the active pharmaceutical substance. It determines the performance of crystalline material and the efficiency of production operations such as filtration and drying. What is more, it also affects the material stability during storage.

How to get the required particle size?

Preferred method of crystallization

During the crystallization process, the crystal size reflects the effect of simultaneous interaction phenomena such as nucleation, crystal growth, agglomeration, which can be disturbed by processing and equipment parameters. Therefore, the control of process parameters such as temperature profile, seed amount and temperature, particle size of seed, antisolvent addition rates, agitation rates are very important in the initial stage of crystallization development and optimization of crystallization. The real-time particle size control using focused beam reflectance measurement (FBRM), as well as in-situ attenuated total reflection Fourier transform infrared spectroscopy (ATR FT-IR) is very useful in crystallization process monitoring and control the PSD of material. In the case of seeds, it is crucial to investigate and determine the metastable zone. Basically, the use of seeds allows for process repeatability, thus limiting the process variability. However, in some cases it is not possible to obtain the appropriate PSD directly from the crystallization process on a production scale.

Other methods

Mechanical size reduction of solids is frequently used to achieve API particle size control. The crystal size reduction can be performed with enough energy to break individual crystals or agglomerates during formulation process. The mechanical reduction of crystals size leads to crystal surface damage thereby can cause the formation of an amorphous phase, polymorphic transformation as well as variations in the crystal size during storage of the material. In many cases, the mechanical reduction of size is difficult due to the high hardness of the crystal making it impossible to downsize the crystal size. Also, the mechanical treatment of hydrates, especially in stoichiometric and non-stoichiometric channel hydrates is problematic.

How it is managed at Polpharma?

Polpharma API has plenty years of experience in delivering APIs with the right particles size distribution through crystallization, milling/micronization, vibration sieving or other technologies. The method is chosen depending on the needs. Variety of equipment and highly educated team with many years of practice allow us to offer APIs with the desired size of particles expected by our customers. Development and optimization of the required PSD begins in the Research and Development Department. It is led by Experts from Solid States Chemistry team, which also supports the entire product lifecycle. To optimize the crystallization process at an early stage with a small amount of material, we use Crystalline that provides information on the shape and size of particles. The Crystalline it also very helpful in determining the width of the metastable zone. To explore the crystallization process on a larger laboratory scale, we use reactors with precise control of temperature gradients and stirring speeds. In addition, we support the crystallization process with an FBRM probe to control the shape and size of particles. The Solid State Chemistry team is involved in developing, scaling-up and implementation of crystallization process and solves any issues appearing during the production. This team works closely in cooperation with Experts from Process Engineering Team, who takes care of products at Polpharma API.

Right Particle Size Distribution directly from Crystallization

The crystallization is one of the main ways of getting the desired particles size distribution. Various types of agitators (e.g. anchor, propeller, impeller) with adjustable stirring speed and numerous crystallization lines up to 6000 dm3 with advanced automated systems, for proper control and monitoring of the defined key crystallization process parameters, give us possibility to get the desired size of particles directly from crystallization. Based on R&D recommendations, appropriate process parameters are applied during the routine manufacturing. The desired PSD can be achieved by changing the key process parameters, such as the type of agitator, stirring speed, concentration, cooling rate, usage of seeds with appropriate PSD etc.

Micronization, Milling or Sieving as alternative techniques

Instead of getting the desired PSD directly from crystallization, other technologies like micronization, milling or vibration sieving are also commonly applied at Polpharma API. Depending on the needs, one of the above mentioned techniques is used. For the most complicated cases, the statistical methods of design of experiments (DoE) are applied, according to QbD approach. There are many useful designs used for defining the optimum of the process e.g. Central Composite Design (CCD), Box-Behnken Design (BBD) or Factorial Designs (FD). Such approach guarantees the process robustness and ability to get the desired particle size distribution "for the first time" and in the repetitive manner.

Micronization, one of the most commonly used method for particle size reduction

The micronization process allows to reduce the particle size of API to micrometer size highly increasing the substance surface. This technique is especially dedicated for the heat-sensitive products, because the temperature remains relatively constant throughout the whole process. Particle size reduction during the micronization occurs without any mechanical components intervention, but using a pressurized process gas to impart high velocity to the particles and determine high energy impacts between the particles. Particle size reduction is finally the result of the particles collisions inside the micronization chamber. The main micronization parameters are the feed rate, the pressure of Venturi nozzle and the pressure in the micronizer chamber. Their proper setting allows to obtain the expected particle size reduction. Polpharma API has two jet-mill micronizers in the manufacturing area and one in the Pilot Plant scale. All of them work in full cGMP environment. Micronizer available at Pilot Plant is used especially for the preparation of different size of particles for our customers for their first stability and bioavailability tests, and for the first formulation runs. Based on this research, the right particle size, suitable for customer's needs, is specified.

Milling and Vibration Sieving also useful techniques

Milling and vibration sieving are also techniques commonly used at Polpharma API for the powder processing operations. The milling is mainly applied to a slight particle size reduction (above 10 microns). For this purpose, different types of mills available at Polpharma are used such as pill mills, classifier mills, etc. The vibration sieves are especially applied when specific fraction with narrow particle size distribution is expected. Polpharma API has two vibration sieves working in full cGMP environment.

Methods of particle size distribution analysis

An important challenge is also the choice of the method that allows proper PSD analysis and solving problems associated with crystal/particle morphology. At Polpharma we develop, validate and transfer PSD methods to clients as well as support them in providing solutions in case of any difficulties. Our laboratory is equipped with: Mastersizer 2000 (with dry, wet and micro dispersion unit), Mastersizer 3000 (with dry, wet dispersion unit and Hydro sight - camera used to observe particles in dispersing medium), Symapatec Helos (with Rodos M, Vibri, Quixel, Cuvette dispersion unit). We also support the analysis using optical microscopy and Morphology 4.

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