Secrets of particle size analysis for Pharmaceutical Preparation and Raw material

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The improvement of drug quality is the basic principle for developing overall strategies. For the current evaluation system, dissolution is a top priority, and the particle size of the pharmaceutical preparation has an important influence on the dissolution curve. However, everyone still faces a lot of confusion about particle size analysis. For example, the results of different test conditions are different, but which one is more reliable? Why do some samples have different results from different manufacturers? Whose granular results are closer to "truth"?

1. Why are the results different from different manufacturers?

In general, two reasons lead to the differences in results, one caused by optical path structures and algorithms. The laser particle size analyzer obtains the particle size distribution by inverse calculation of Mie theory using an optical model. However, when developing an instrument, how do you know whether the model you selected is correct? How do you determine whether the detector position and the optical path are reasonable and accurate? The answer is to use spherical standard particles with known particle sizes for research! Therefore, establishing the detection system step by step, each manufacturer determines its own model and algorithm based on spherical standard particles. Generally, the spherical particle diffraction spot is a concentric circle, but the slit diffraction is a set of stripes.

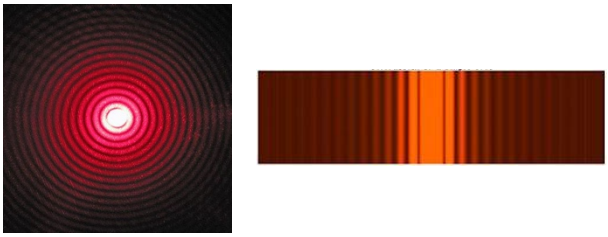
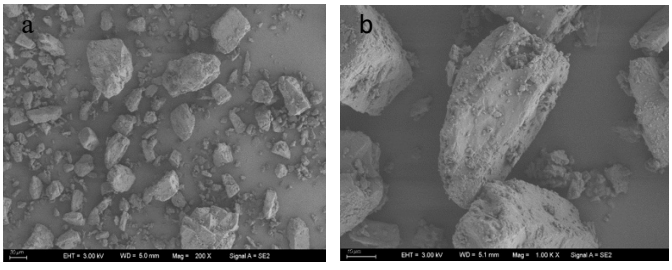


Figure 1. Spherical particle and single slit diffraction spot

What is our real particle like?



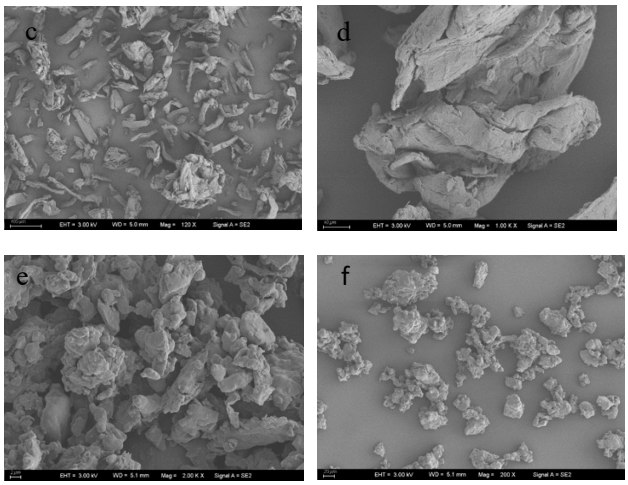


Figure 2. Lactose (a, b), microcrystalline cellulose (c, d), API 1 (e) and API 2 (f)

Various particle shapes are different under this background, rod-shaped microcrystalline cellulose, agglomerated lactose, irregular API, spherical granulation, etc., which means that the diffraction spot is also extremely complicated. Therefore, various differences are generated in particle size results. This is the reason why the results of the spherical standard sample are similar for different manufacturers, but the results of the actual raw material and pharmaceutical preparation are quite different.

Generally, the significant difference may come from the dispersion method. There are two methods to disperse the drug particles, dry and wet. Each instrument will be equipped with a dispersing attachment that disperses the drug particles into individual "particles" to pass through the measurement area. However, due to design, patent, etc., energy delivery of each manufacturer is difference. The circulation pipe, speed and ultrasonic

output may be completely different. Although the output power is same, the structure is different, resulting in a difference in the actual energy to the particles. If the wet method can reduce this difference and risk by introducing external ultrasound, the dry method has no way to avoid this risk, because the dry dispersion is integrated with the instrument. For example, Bettersize disperses the sample with different venturi pipe. The early one is connected by the straight-through pipeline. While another supplier inhales and then disperses the particles by means of “tornado” with negative pressure. These treatments vary in characteristics, which leads to the increase of risk of test results.

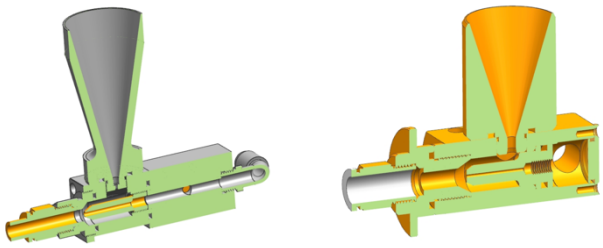


Figure 3. Two different dry dispersion accessories from Bettersize

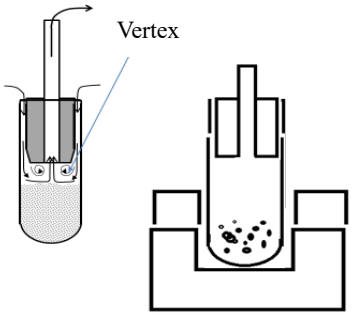


Figure 4. Supplier B dry dispersion accessory

Someone may be confused immediately. No matter what kind of pipeline, as long as the samples are scattered into "small particles", shouldn't the results be close? Indeed, it should be the same in theory, but it is actually not the case. For example, a raw auxiliary powder, if its adhesion is low, the fluidity is perfect, and the distribution is narrow, the result should be close and be similar to the wet method. However, if your sample is "comparative sticky", "poor mobility" and "wide distribution", do you still think that your particle results are the same? For example, can a glass bead sample be the same as drug? That is the reason why when doing drug particle size testing, once you choose a dry method, you must be aware that this sample may be tube-dependent, pressure-dependent, and the differences from different instruments may be large.

The above is the result of the dry measurement of a salt-caving raw material drug. The upper, middle and lower parts of the figure are the results of the A supplier's model 1, model 2 and model 3 dry dispersion accessory, which shows D50 is around 20 microns for model 1 and D50 is around 80 microns for model 2, and the difference of D90 may be even larger. Can you make a conclude which pipe or instrument is better? You have no way to prove it. Three results have been pressure titrated and have good precision. Someone will think that the results can be confirmed by images. However, it is difficult to determine the sample size through the image method whose size is between less than 1 micron and up to several hundred micrometers, because the range is similar, but the ratio is very different. How do you determine it? Is the “peak” in front of the particle size distribution reasonable? Unsure, this is the current situation for dry method.

2. How do you deal with this situation as a manufacturer of pharmaceutical preparations or raw materials?

How should we face and deal with this matter under the above situation? No matter which manufacturer, they can’t prove that their results are "perfect", "close to the truth". Because lactose is not a spherical standard sample, its morphology is different and the results are almost the same through image method, can you explain that 8 microns is more accurate than 8.5 microns? How should I do it? Firstly, we should understand why we should measure these particles? There are two reasons for this. One is that particle size has a great influence on the production process, including mixing, tableting, dissolution and BE, so we have to test and control the particle size. Another is that customers need specification of particle size, so we have to compare the data. If you were the supplier, we should consider whether the accuracy of this test result is sufficient, whether the results can reflect the changes or the correlation of the production process.

To give you a simple example, if we put the original drug and the generic drug together, can the instrument objectively give the difference between the two samples? The lactose of the two different processes has a certain difference, can the instrument correctly distinguish them under the condition of ensuring accuracy? In other words, can the instrument distinguish between different samples? Are the results measured by instrument consistent for two close sample? For the same sample, it is meaningless to examine the difference between different manufactures, which can’t solve the problem fundamentally. Is it that we only need to carry out the precision test and don’t need

consider accuracy? Of course not, what should I do? Methodology and verification must be performed carefully.

3. How to do methodology and verification?

The methodology is to study all the influencing factors, identify critical quality attributes (CQA) that may affect testing results, and then evaluate and confirm these factors. After confirming the conditions, a series of verifications should be performed, including precision verification and cross-verification.

For the factor of ultrasound, we can study the effects of different ultrasound times (1min, 2min, 3min, 5min...) and different ultrasonic power (30w, 50w, 100w...) on the results. For the obscuration factor, we can study the effect of different obscuration (3%, 7%, 10%, 15%, 20%...) on the results. Sometime according to the characteristics of the sample, the factor of sampling method, circulation, pressure, PH, surfactant and dispersant also be considered. At the same time, through image technology, photoresist counter technology, etc., to check the rationality of the results.

4. How to choose dry method or wet method?

Powder can be tested either by suspension dispersion or by air pressure dispersion testing, so customers are confused about how to choose dry or wet method. In fact, these two methods can be adopted in the Pharmacopoeia, but how to choose these two methods and reduce the risk? Some people think that powder should be measured by dry method, wet measurement, stress that wet method may change the crystal form of the particles, surfactant is easy to produce bubbles, if the use of solvents will produce waste, the influencing factors are difficult to control. The dry sample wet test theory emphasizes that the dry test is easy to “break” the particles, the fine powder is “not blown”, and the control factors are less.

Some people think that the powder should be measured by dry method, because the medium may change the crystal form of the particles and bubbles are easily generated from the surfactant. If the solvent is used as the medium, the waste will be generated after the measurement and the factors that affect test results will increase. The people who think that the powder should be measured by wet method emphasizes the dry method is easy to “break” the particles, the fine powder is not easy “dispersed”, and the ways of controlling risk are less. However, I don't think the above points are objective. For example, a drug tablet needs to be released and absorbed in the stomach, that is in a wet environment. When we still adopt the dry method to obtain the result, can we say it is more reasonable? On the other hand, it is difficult to find a good solution or solvent to suspend the particles for the wet method. What if the surfactant produces solubilization or bubbles? What if different raw materials have different solvents? What if the raw materials dissolve or dissolves slightly in the solvent?

In fact, suppliers will promote instrument based on the advantages of their products. How can we avoid the misleading from suppliers? Although the final result is not absolute, we should determine the measurement method according to the property of the sample, the condition of application and the advantages and disadvantages of the dry and wet methods. Each decision should be made based on data. Of course, we should refer to the relevant companies and previous practices, which can save our time.

The advantages of dry method	The advantages of wet method
1. Fast measurement 2. Dispersed by air, don’t need consider dispersant medium and other organic solvents 3. Representativeness is good 4. The measurement is simple and the factors that affects the result are small. 5. Don’t consider solvent recovery	1. The particle can be tested in the circulation system 2. The ways of dispersion are flexible, including circulation, ultrasonic and different medium 3. Good choice for fine particle 4. High data stability 5. Application is wide
The disadvantages of dry method	The disadvantages of wet method
1. Poor dispersion for fine particle 2. Have the risk of breaking particle 3. Result depends on pipe design 4. Control factors are low 5. High reproducible is difficult	1. Consider solvent recovery for solvent medium 2. The sample may dissolve or change in the medium 3. Factors that affect the results are too much

In the face of increasingly strict supervision and changes in the situation, I hope that our pharmaceutical companies can effectively improve the quality of the drugs. Only the quality of drugs is getting better, can our company develop more stable.