# Research on Particle Sizing Dispersion Methods of Domperidone API by Laser Particle Size Analyzer

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**Abstract:** Objective: To establish the optimal particle sizing dispersion method for Domperidone API by laser diffraction. Method: Using Bettersizer 2600, an automatic laser particle size analyzer with both dry and wet dispersion system, to systematically study the particle size distribution of Domperidone API. The research investigated the impact of dispersing intensity on the particle size analysis, including different air pressures of dry dispersion, different stirring speeds and ultrasonic dispersing time of wet dispersion. Conclusion: By comparing the test results of both wet and dry dispersion methods, the wet dispersion method is recommended since it can provide more accurate results and more reasonable data correlation.

**Key words**: Laser diffraction; Particle size analyzer; Domperidone API

Domperidone that acts primarily on the chemoreceptor triggering region outside the blood-brain barrier, as the representative of the second generation of gastroprokinetic agent, is a synthetic benzimidazole derivative. It is a dopamine receptor blocker with anti-vomiting effect by blocking peripheral dopamine receptors, thereby enhancing the stomach motility and increasing the lower esophageal sphincter pressure. Domperidone is widely used in the treatment of flatulence, esophageal reflux, and vomit caused by chemotherapy. Since the solubility of the Domperidone particles has great influence on the absorption in the body, it is necessary to examine the influence of the particle size on the product quality. The difference of particle size distribution among batches could lead to inconsistency in dissolution and body absorption; furthermore, affect the efficacy and safety of drugs directly. Therefore, the effect of particle size distribution on product quality must be researched.

The USP has clear regulations on API particle sizing by laser diffraction method, such as the structure and principle of the instrument, the specific method of dry and wet dispersions, the factors in the measurement process, etc. However, for specific drugs, there is no related instruction on how to evaluate and choose wet or dry dispersion method. This paper carried out a systematic research on how to choose dispersion method when measuring particle size distribution of Domperidone API in accordance with the USP and the ISO 13320.

## 1. Experiment

### 1.1 Instruments

- Bettersizer 2600 laser particle size analyzer from Dandong Bettersize Instrument Ltd;
- MS303S electronic scale from Mettler Toledo;
- SC ultrasonic cleaner from Shanghai Shengyan Ultrasonic Instrument Co.,Ltd.

### 1.2 Sample and reagent

Two sets of Domperidone API sample:

- No.1: non-micronized sample (batch No.0068116-17);
- No.2: micronized sample;

Tween 80 for analytical reagent; Purified water.

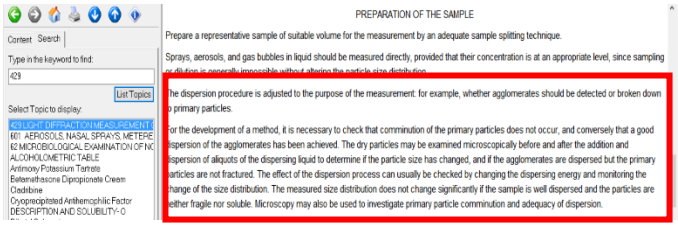
## 2. Particle size distribution measurement and method evaluation

### 2.1 Dry dispersion method

#### 2.1.1 Study on the methodology of dry dispersion method

Dry dispersion is to transport powder particles by compressed air, disperse powder particles by collision of particles and particles, collision of particles and pipe, and airflow shear.

API powder was composed by small organic molecules particles, which could break under the shear stress and collision. In order to ensure the dispersal of large agglomerate without breaking the original particles, the USP requires investigating the effect of different dispersive intensity on test results (USP 429):




In dry dispersion experiments, we investigated the effect of dispersed pressure on the particle sizing results. The dispersed pressure ranged from 0.05Mpa to 4Mpa, and a set of data was tested every 0.5bar.

Abscissa: dispersion pressure; Ordinate: particle size; Blue curve: D10; Orange curve: D50; Grey curve: D90.

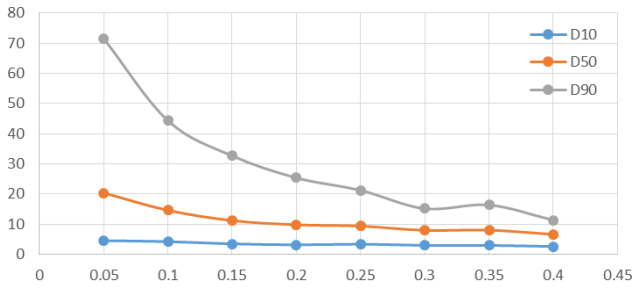



**Figure 1.** Particle size pressure titration data of non-micronized sample

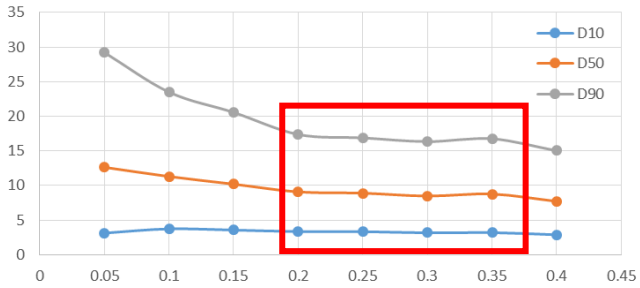



**Figure 2.** Particle size pressure titration data of micronized sample

The ideal pressure titration curve, as the dispersed pressure increases, the particle size gradually decreases, and the curve gradually reaches a stable period. If pressure increases further, the curve will go further downward, which corresponds to the gradual dispersal of large agglomerate to single particles. If the pressure is further increased, the drug particles could break. However, the difficulty of drug particle sizing is that there is no strict boundary between aggregate dispersion and single particle breakage, so further experiments are needed.

Figure 2 showed that there was an obvious "stable platform" of the micronized sample, which represented the results between 0.2 Mpa and 0.35 Mpa. However, when increasing the pressure of the non-micronized sample, there was no "stable platform" and particle size of the sample decreased continuously, which was generally the signal of the particle breakage.

For further diagnosis, we captured the image of non-micronized sample (Figure 3), which shown that the sample was semitransparent irregular crystal particles. Judging from the state, the sample was easy to break. When increasing the dry dispersion pressure, the risk of particle breakage would increase consequently.

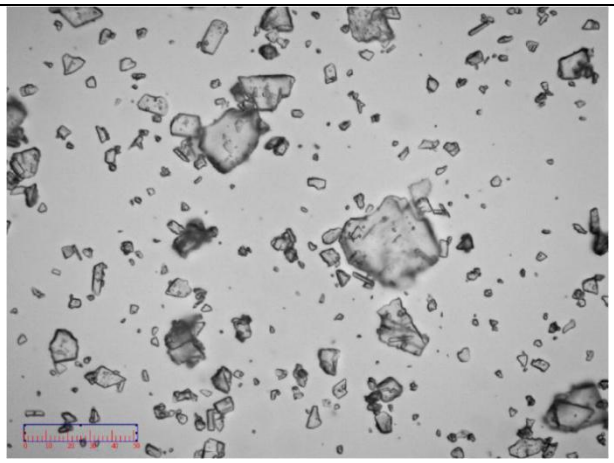


**Figure 3.** Image of non-micronized sample

In order to further determine the appropriate dry dispersion pressure, the particle size distributions of non-micronized samples were tested under different pressures (Figure 4).

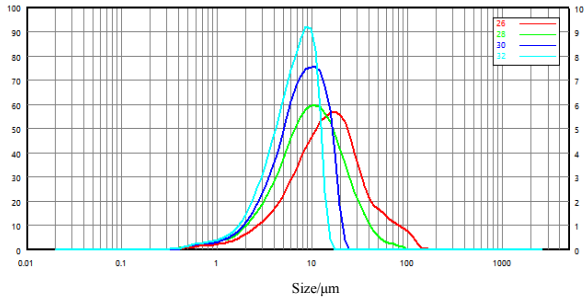



**Figure 4.** Particle size distribution of non-micronized sample under different pressures: red, green, navy, and cyan curve respectively represent 0.1, 0.2, 0.3, and 0.4 Mpa

The results indicated that with the increase of dispersion pressure, the maximum particle size decreased from 150-100 μm to 30-20 μm. The image proved the existence of few coarse particles with size around 100 μm. Furthermore, these coarse particles could be identified as single particle instead of agglomerated ones (Figure 5-6).

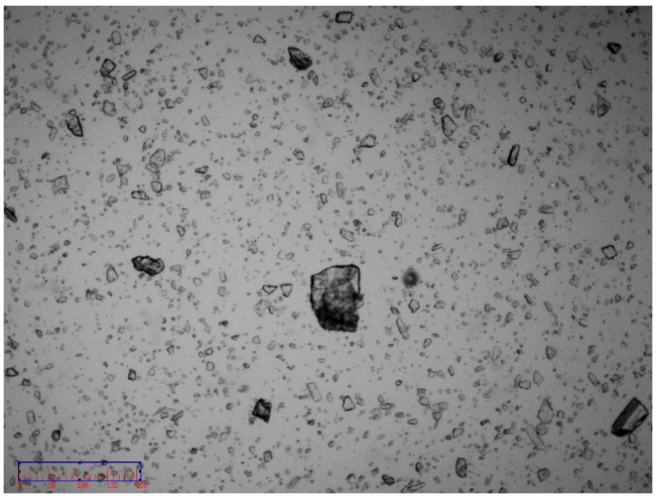


**Figure 5.** Image of non-micronized particles

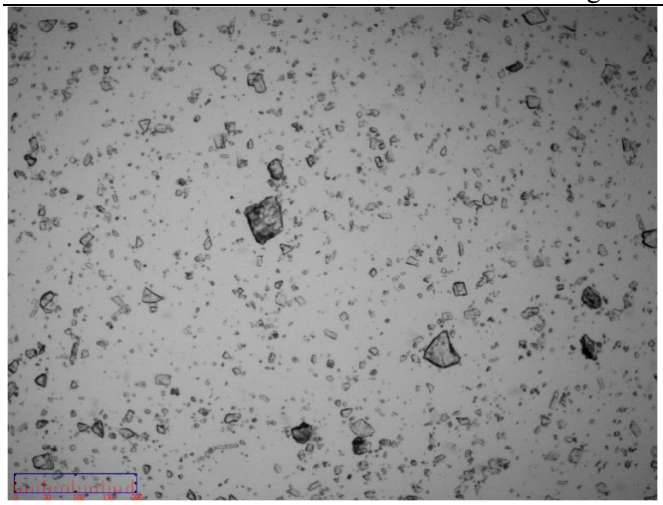
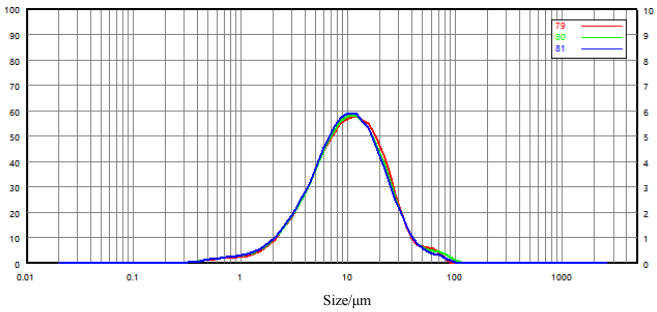


**Figure 6.** Image of non-micronized particles

It was not factual that the maximum particle size is 30-20 μm. Therefore, we could reach the conclusion that the particles were broken when dispersion pressure reached to above 0.3 Mpa. Considered the pressure titration curve (Figure 2) and the fragility of the sample itself, 0.2 Mpa was selected to test particle size distribution of Domperidone API.

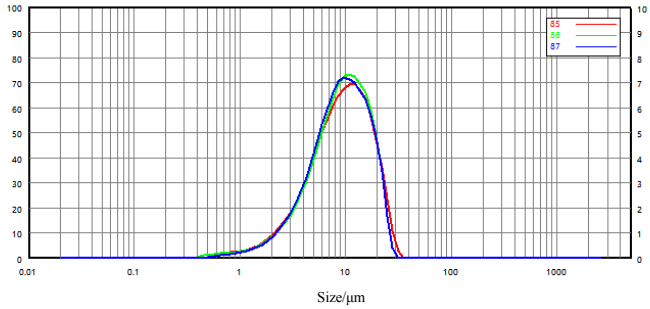
### 2.1.2 Research on the precision of dry dispersion method

Based on the above experiments, Domperidone API was measured under dispersion pressure 0.2 Mpa. Figure 7 & 8 shown the particle size distribution curves and repeatability data of non-micronized and micronized samples. The repeatability results for both samples far exceeded the requirements of the USP: repeatability of D50 was smaller than 2.1% while those of D10 and D90 were smaller than 3.5%, which proved that the dry dispersion method was reliable to measure particle size distribution of Domperidone API.




| Number | Sample | D10/μm | D50/μm | D90/μm |
|---|---|---|---|---|
| 79 | 0068116-17 non-micronized-0.2 | 3.332 | 10.31 | 26.44 |
| 80 | 0068116-17 non-micronized-0.2 | 3.222 | 10.13 | 26.79 |
| 81 | 0068116-17 non-micronized-0.2 | 3.157 | 9.905 | 25.91 |
| RSD | | 2.73% | 2.01% | 1.68% |

**Figure 7.** Particle size distribution and repeatability of non-micronized particles (dry dispersion)



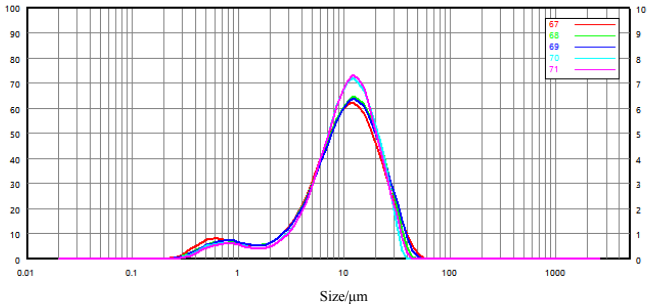

| Number | Sample | D10/μm | D50/μm | D90/μm |
|---|---|---|---|---|
| 85 | 0068116-17 micronized-0.2 | 3.274 | 9.341 | 19.27 |
| 86 | 0068116-17 micronized-0.2 | 3.398 | 9.377 | 18.63 |
| 87 | 0068116-17 micronized-0.2 | 3.505 | 9.174 | 18.60 |
| RSD | | 3.41% | 1.17% | 2.01% |

**Figure 8.** Particle size distribution and repeatability of micronized particles (dry dispersion)

## 2.2 Wet dispersion method

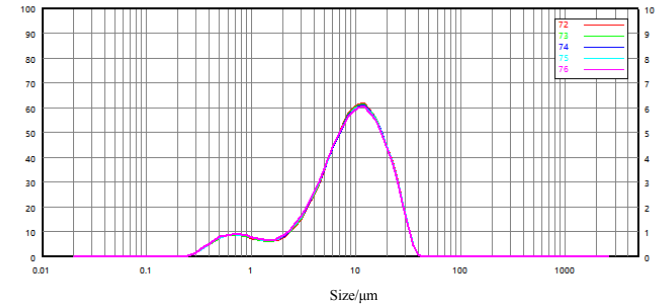
### 2.2.1 Study on the methodology of wet dispersion method

Domperidone API is insoluble in water. After wetted by surfactant, sample was dispersed in water by stir and ultrasonic dispersion. Due to its fragility, the dispersion intensity should be low. At the same time, in order to investigate the influence of dispersed intensity on sample particles, two dispersion methods: stir and ultrasonic dispersion were applied respectively (Figure 9 & 10).




| Number | Sample | D10/μm | D50/μm | D90/μm |
|---|---|---|---|---|
| 67 | 0068116-17 micronized-B | 2.066 | 10.14 | 24.21 |
| 68 | 0068116-17 micronized-B | 2.481 | 10.49 | 23.71 |
| 69 | 0068116-17 micronized-B | 2.514 | 10.62 | 24.57 |
| 70 | 0068116-17 micronized-B | 3.127 | 10.63 | 22.06 |
| 71 | 0068116-17 micronized-B | 3.297 | 10.74 | 22.54 |
| RSD | | 18.75% | 2.21% | 4.61% |

**Figure 9.** Test sample particle size distribution under agitation only




| Number | Sample | D10/μm | D50/μm | D90/μm |
|---|---|---|---|---|
| 72 | 0068116-17 micronized-C | 1.719 | 9.200 | 21.35 |
| 73 | 0068116-17 micronized-C | 1.716 | 9.154 | 21.31 |
| 74 | 0068116-17 micronized-C | 1.660 | 9.120 | 21.32 |
| 75 | 0068116-17 micronized-C | 1.666 | 9.089 | 21.32 |
| 76 | 0068116-17 micronized-C | 1.616 | 9.031 | 21.25 |
| RSD | | 2.57% | 0.70% | 0.17% |

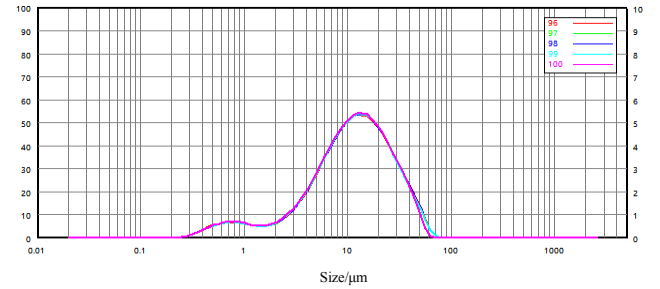
**Figure 10.** Test sample particle size distribution after stir dispersion only

From Figure 9 & 10, we could find out that the results were not stable when sample was only stirred. Besides, considered the characteristics of wet dispersion, the drug particles could still be adherent. But the stability was greatly improved after the low intensity ultrasonic dispersion. Meanwhile, ultrasonic had little influence on the particle size distribution. Its main effect was on large particle trailing. The repeatability of testing results under low intensity ultrasonic dispersion was greatly improved, so the subsequent wet dispersion adopted the low-intensity ultrasonic method.

### 2.2.2 Research on the precision of wet dispersion method

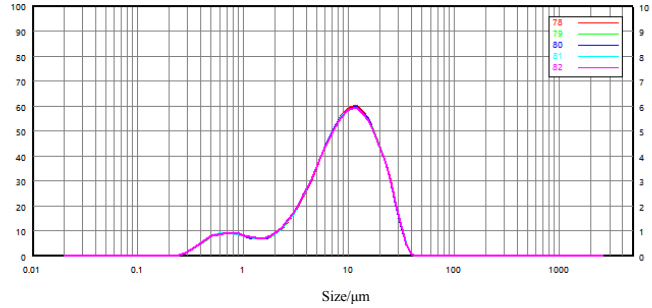
Keep the above conditions unchanged, we investigated the precision of particle size distribution data when sample was dispersed by low-intensity ultrasonic.

Figure 11 and 12 indicated the particle size distribution and repeatability data by wet dispersion of the non-micronized and micronized samples. Compared with the dry dispersion, the repeatability was greatly improved: the relative deviations of D50 and D90 were below 0.7%, and that of D10 was below 2.6%. It proved that the wet dispersion was more reliable than dry dispersion when measuring particle size distribution of Domperidone API.




| Number | Sample | D10/μm | D50/μm | D90/μm |
|---|---|---|---|---|
| 96 | 0068116-17 non-micronized-C | 2.632 | 11.68 | 32.51 |
| 97 | 0068116-17 non-micronized-C | 2.640 | 11.69 | 32.29 |
| 98 | 0068116-17 non-micronized-C | 2.627 | 11.66 | 32.30 |
| 99 | 0068116-17 non-micronized-C | 2.615 | 11.60 | 31.96 |
| 100 | 0068116-17 non-micronized-C | 2.552 | 11.44 | 30.91 |
| RSD | | 1.35% | 0.89% | 1.99% |

**Figure 11.** Particle size distribution and repeatability of non-micronized sample (wet dispersion)



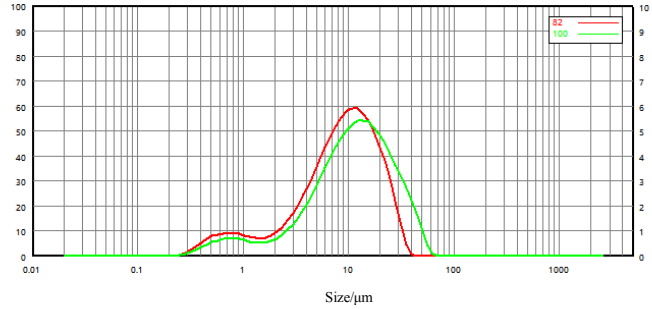

| Number | Sample | D10/μm | D50/μm | D90/μm |
|---|---|---|---|---|
| 78 | 0068116-17 micronized-C | 1.611 | 9.008 | 21.29 |
| 79 | 0068116-17 micronized-C | 1.595 | 8.971 | 21.28 |
| 80 | 0068116-17 micronized-C | 1.579 | 8.945 | 21.22 |
| 81 | 0068116-17 micronized-C | 1.570 | 8.944 | 21.28 |
| 82 | 0068116-17 micronized-C | 1.561 | 8.916 | 21.23 |
| RSD | | 1.26% | 0.39% | 0.15% |

**Figure 12.** Particle size distribution and repeatability of micronized sample (wet dispersion)

## 2.3 Compare and evaluate dry and wet dispersion methods

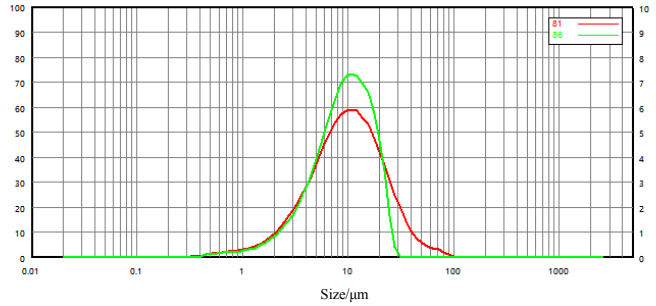
First of all, in terms of test precision, wet dispersion was obviously better than dry dispersion. It was mainly because particles passed the test area only once for dry dispersion, while passed repeatedly for wet dispersion, which provided a higher sampling frequency of wet dispersion.

Secondly, from the perspective of relative rationality of data, Figure 13 & 14 were the particle size distribution data of non-micronized and micronized sample by dry and wet dispersion methods. For wet dispersion method, the particle size distribution peak moved to small particles after micronization. D10, D50, and D90 all decreased with different extents. However, for dry dispersion method, large particles changed greatly before and after micronization, while fine particles rarely changed.




| Number | Sample | D10/μm | D50/μm | D90/μm |
|---|---|---|---|---|
| 82 | 0068116-17 micronized-C | 1.561 | 8.916 | 21.23 |
| 100 | 0068116-17 non-micronized-C | 2.552 | 11.44 | 30.91 |

**Figure 13.** Compare particle size distribution results before and after micronization (wet dispersion)




| Number | Sample | D10/μm | D50/μm | D90/μm |
|---|---|---|---|---|
| 81 | 0068116-17 non-micronized-0.2 | 3.157 | 9.905 | 25.91 |
| 86 | 0068116-17 micronized-0.2 | 3.398 | 9.377 | 18.63 |

**Figure 14.** Compare particle size distribution results before and after micronization (dry dispersion)

## 3. Conclusion

Overall, for particle size distribution measurement of Domperidone API, both wet and dry dispersion methods could provide high precision results. However, since Domperidone API is fragile, adequate data support is required for sample dispersion, especially for dry dispersion method.

Compared with dry dispersion, wet dispersion was observed to provide data with better repeatability, correlation, and rationality.

Therefore, wet dispersion method is relatively reasonable to analyze particle size distribution of Domperidone API.

### Reference

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