IMPORTANT ROLE OF PSD PARAMETER IN API AND FORMULATION ORAL DOSAGE

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ABSTRACT
PSD is one of the important parameters in APIS, because after API, the next step will be formulation. It is not a matter of sterile dosage but the oral dosage form PSD parameter that is the main concern. So, purity and all other things are under the same limits, exclusive of PSD. It will have an effect on dosage uniformity, dissolution rates, and bioavailability. So, PSD is a link between API and formulation. If the thing is higher than the limits, it is easy to take by material milling followed by passing through different meshes, but if the thing is lower than the limits, bringing it to the limits is difficult. As a result, lower limits on the material must be processed for enhancement. Lower PSD limits are taken to limits mainly by slow distillation, re-crystallisation, anti-solvent, and polymorphism with minimum yield loss by commercially viable methods.

Key Words: *PSD (Particle size Distribution) Enhancement, slow distillation method, Oral Dosage.*

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INTRODUCTION

To introduce the concept of "particle size distribution", "particle size" must first be defined. The shape of almost all particles cannot be simply and quantitatively expressed as "spheres" or "cubes." Particles are complex and irregular shapes, and their particle size cannot be directly defined. This is why the indirect definition "sphere-equivalent diameter" is used. Under this definition, when a certain particle is measured based on a certain principle of measurement, the particle size of the measured particle is expressed by the diameter of a spherical body that displays the same result (i.e. measurement quantity or pattern). For example, with the "precipitation method," the particle size of the particle to be measured having the same precipitation velocity as a sphere of diameter 1 µm of the same substance as the particle to be measured is assumed to be 1 µm. However, with the "laser diffraction/scattering method," the particle size to be measured shows the same diffracted/scattered light pattern as a 1 µm-diameter sphere is 1 µm regardless of the shape of the particle.

METHODS OF PARTICLE SIZE DISTRIBUTION ENHANCEMENT

1. **Low RPM Distillation:**
   Take any material with small particles and completely dissolve it in any suitable solvent at different temperatures and distil with low RPM to get a higher range of PSD. For example, in Malvern particle size analysis, the material of small PSD where the D90 value is 20 to 30 µ in size is considered. First, it is supposed to dissolve in methanol at any temperature, and then it is distilled at a very low RPM (70/min) at any temperature to get a higher PSD. Assume that the PSD of the one distilled at 60 ºC increases by 20 to 90 µ, that distilled at 40 ºC increases by 20 to 270 µ, and that distilled at 35 ºC increases by 20 to 430 µ. So this method easily achieves PSD enhancement as well as no loss of material and solvent on a commercial scale.
2. **Anti-Solvent or Polymorphism**
   This method achieves enhancement of PSD and purity as well. Take any small size particle material and dissolve it completely in any solvent in reflux temperature and add anti-solvent very slowly at low RPM, for example, to such a material dissolved in Chloroform solvent after heating to 60 ºC add anti-solvent of Acetonitrile, drop by drop, at 60 ºC at low RPM followed by gradually cooling it to 0-30 ºC, and then filtered (do not crush).
3. **Semi-Dry**
   Take any small size particle material and make it semi-dry material. This means the use of suitable solvent to spray on the material to make little wet. Then sieve through mesh depending on size requirements like 20, 40, 60…..430, etc., and thereafter the sieved material is dried under vacuum. This achieves easy recovery of solvent and PSD enhancement without loss.
4. **Re-crystallisation**
   Take any small-particle material and dissolve completely in any suitable solvent at reflux temperature then re-precipitate at slow RPM and slow cooling followed by filtration and then dry.
5. **High Vacuum Distillation**
   This is only applicable for low melting materials. Take the material and perform HVD (high vacuum distillation). This Means material is distilled to its boiling point by using a vacuum and then collected. It gives highly pure and valued material with high PSD.

Experiment Report of Different PSD Values:

Silica is prepared from 40% sodium silicate and sulphuric acid combination in water, then part isolated through distillation at different temperatures to get a different grade or size of silica.

Table-1: Table of approximate PSD values

Sl. No.	Distillation Temperature	PSD (D90) value
1	95°C-100°C	270µ
2	85°C-90°C	330µ
3	75°C-80°C	420µ
4	65°C-70°C	820µ
5	55°C-60°C	Immeasurable
6	45°C-50°C	Immeasurable
7	35°C-40°C	Like stone

PSD Importance of API and Formulations:

New drug development is a long and arduous process - many complicated steps are involved in identifying, developing and incorporating a new active pharmaceutical ingredient (API) into a suitable dosage form. Among

other factors, certain physical characteristics of APIs determine their relevant properties. Particle size is arguably the most important of these variables.

Particle Size Matters in API

Adjustments in particle size may alter related properties, such as shape, surface area and porosity. This, in turn, can affect everything from bio-availability to shelf stability. Given the increasingly potent APIs being developed, smaller particle sizes are typically more desirable in today's pharmaceutical marketplace. Not surprisingly, then, particle size is the property most frequently monitored during the pharmaceutical development and manufacturing process.

Properties such as particle size distribution curves, particle shape and particle surface characteristics also influence the behaviour and suitability of a drug formulation. Surface characteristics, will influence flowability, compact ability and hygroscopicity. These properties are of great interest to process engineers, as they may significantly affect pharmaceutical manufacturing processes, such as milling, wet granulation and encapsulation.

Particle Size Matters in Formulations

Tightly controlled particle size distributions are highly important for pharmaceutical drug development. Powder particle size distribution is a valuable indicator of quality and performance. After all the hard work is done to research and develop a new pharmaceutical drug, the next step towards manufacturing is to identify the best way to get the new active pharmaceutical ingredient (API) into a suitable dosage form.

The flowability and ease of handling of the API and excipients (fillers and lubricants) are key requirements for the drug formulation. Dissolution rates, uniformity and consistency of the drug content are the most important parameters for drug effectiveness, quality, and most importantly, bioavailability. Bioavailability is a term used in pharmacology, referring to the degree and rate at which an administered drug is absorbed by the body's circulatory system.

The impact that pharmaceutical particles and powders have on bioavailability and performance is tested and evaluated at multiple different phases during the development of all drugs. Once the impact has been analysed during the final development phase, target particle size distribution specifications are determined to control manufacturing consistency and drug product quality.

Formulations are a very important aspect of creating medicines since they are essential in ensuring that the active part of the drug is delivered to the correct part of the body, in the right concentration, and at the correct rate (not too fast or too slow).

Table-2 Particle Size Conversion Table

Particle Size Table

SIEVE MESH	OPENING		
U.S. Mesh	Inches	Microns	Millimeters
Millimeters			
3	.265	6730	6.73
3.5	.223	5660	5.66
4	.187	4760	4.76
5	.157	4000	4.00
6	.132	3360	3.36
7	.111	2830	2.83
8	.0937	2380	2.38
10	.0787	2000	2.00
12	.0661	1680	1.68
14	.0555	1410	1.41
16	.0469	1190	1.19
18	.0394	1000	1.00
20	.0331	841	.84
25	.0280	707	.71
30	.0232	595	.59
35	.0197	500	.50
40	.0165	420	.42
45	.0138	354	.35
50	.0117	297	.297
60	.0098	250	.250
70	.0083	210	.210
80	.0070	177	.177
100	.0059	149	.149
120	.0049	125	.125
140	.0041	105	.105
170	.0035	88	.088
200	.0029	74	.074
230	.0024	63	.063
270	.0021	53	.053
325	.0017	44	.044
400	.0015	37	.037

Methods in Measurement Techniques

1. Sieve analysis
2. Air elutriation analysis
3. Photo-analysis
4. Optical counting methods
5. Electrical resistance counting methods
6. Sedimentation techniques
7. Laser diffraction methods
8. Laser Obscuration Time (LOT) &/or Time of Transition (TOT) analysis
9. Acoustic Spectroscopy or Ultrasound Attenuation Spectroscopy
10. Air pollution emissions measurements and Malvern particle size analysis

Common Industry method of Malvern particle size analysis for measurement of D10, D50, and D90:

There is a range of sizes present, which is mathematically described by a distribution.

There are different ways to represent this distribution in terms of:

1. Intensity – How much light comes from the different components?
2. Volume or mass – How much volume is present in the different components?
3. Number – How many particles are present in the different components?

This often causes confusion, and the intensity volume number issue is one of the most popular blogs.

Intuitively, the easiest to understand is the volume distribution: we have so many cups, mL or µL of component A and so many of component B. If there is a range of components, i.e. sizes, then one simple way to explain a distribution is by specifying how much material is present up to a certain size.

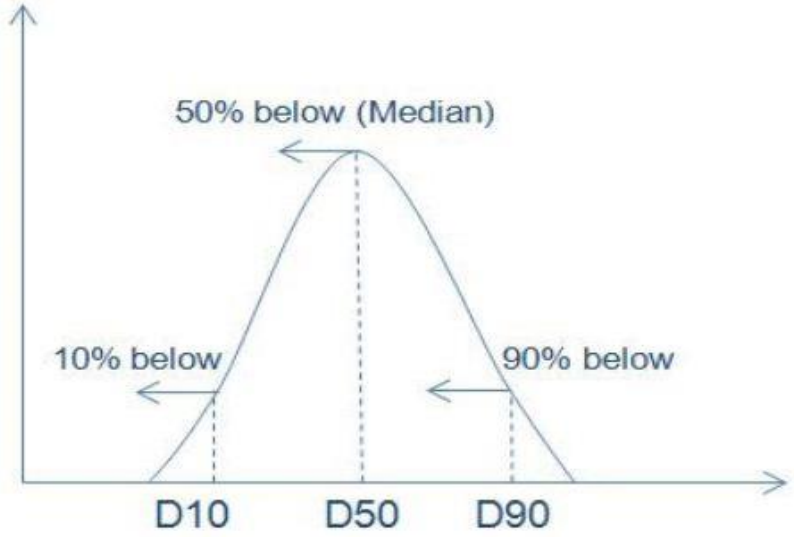
The parameter D90 should more correctly be labelled as Dv(90). It signifies the point in the size distribution, up to and including which, 90% of the total volume of material in the sample is 'contained'. For example, if the D90 is 844nm, this means that 90% of the sample has a size of 844nm or smaller. The definition for D50 or Dv(50 is then the size point below which 50% of the material is contained. Similarly, the D10 or Dv(10) is that size below which 10% of the material is contained. This description has long been used in size distribution measurements by laser diffraction.

An additional parameter to show the width of the size distribution is the span. The span of a volume-based size distribution is defined as **Span** = **(D90 – D10)/D50** and gives an indication of how far the 10 percent and 90 percent points are apart, normalized with the midpoint.

RESULT AND CONCLUSION

Do not take this small parameter lightly; it is a link between API and formulation. Higher size is not a problem because it is obtained through milling, but lower size is extremely difficult to make higher. Following the different methods to get the perfect result is important. So this work is useful for PSD enhancement.

Figure - 1: Malvern particle size Analyzed Chromatogram



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