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PARTICLE-SIZE DISTRIBUTION ESTIMATION BY ANALYTICAL SIEVING

6 Sieving is one of the oldest methods of classifying powders and granules by particle size
7 distribution. When using a woven wire cloth, the sieving will essentially sort the particles by their
8 intermediate size dimension (i.e., width or thickness). Sieving by mechanical agitation is most
9 suitable where the majority of the particles are larger than about 75 μm . For smaller particles,
10 gravitational separation and agitation provide insufficient force to overcome particle cohesion and
11 adhesion during the sieving process, causing particles that would be expected to pass through a sieve
12 to be retained. For such powders or granules, other means of agitation such as air-jet sieving or sonic
13 sifting may be more appropriate. Nevertheless, mechanical sieving can sometimes be used for some
14 powders or granules having median particle sizes smaller than 75 μm where the method can be
15 validated. In pharmaceutical applications, sieving is usually applied for classification of the coarser
16 grades of powders or granules. This method has particular advantages in that powders and granules
17 are classified mainly on the basis of particle size, rather than other properties e.g. sedimentation or
18 light scattering, and in most cases the analysis can be carried out in the dry state.

19 The limitations of sieving include the need for an appreciable amount of test sample (normally
20 at least 25 g, depending on the density of the powder or granule, and the diameter of test sieves) and
21 the difficulty in sieving adhesive or cohesive powders or granules that tend to clog the sieve
22 apertures. The method is essentially a two-dimensional estimate of size because passage through the
23 sieve aperture is frequently more dependent on maximum width and thickness than on length.

24 This method is intended for estimation of the particle size distribution of a powder or granules.
25 It is not intended for determination of the proportion of particles passing or retained on one or two
26 sieves.

27 The particle size distribution is estimated as described under *Sieving by Mechanical Agitation*,
28 unless otherwise specified in the individual monograph. Where difficulty is experienced in reaching
29 the endpoint (i.e., the powder or granules do not readily pass through the sieves) or when it is
30 necessary to use the finer end of the sieving range (i.e., below 75 μm), consideration must be given
31 to the use of an alternative particle-sizing method as for instance air entrainment or wet dispersing
32 methods.

33 Sieving is to be carried out under conditions that minimize effects related to gain or loss of
34 moisture in the test sample. Thus, it is recommended to control the relative humidity of the
35 environment in which the sieving is carried out. Unless otherwise prescribed, analytical sieving is
36 normally carried out under ambient conditions. Any special conditions that apply to a particular
37 powder or granules are to be detailed in the individual monograph.

38 **Principles of Analytical Sieving**—Analytical test sieves are constructed from a woven wire
39 cloth, which is of simple weave that is assumed to give nearly square apertures and is sealed into the
40 base of an open cylindrical frame. The basic analytical method involves stacking the sieves in
41 ascending aperture size over a collecting pan, and then placing the powder or granule sample to be
42 tested on the top sieve.

43 The nest of sieves is subjected to a standardized period of agitation, and then the powder or
44 granules retained on each sieve is accurately weighed. The test gives the weight percentage of
45 powder or granules in each sieve size range.

46 This sieving process for estimating the particle-size distribution of a powder or of granules is
47 generally intended for use where at least 80% of the particles are larger than 75 μm . The size
48 parameter relevant for determining particle-size distribution by analytical sieving is the length of the
49 side of the minimum square aperture through which the particle will pass.

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59**TEST SIEVES**

Test sieves suitable for pharmacopoeial tests conform to the current edition of International Organisation for Standardization (ISO) ISO 3310 – 1 specification; Test sieves – Technical requirements and testing – Part 1: Test sieves of metal wire cloth. Unless otherwise specified in the monograph, use the ISO sieves listed in Table 1 in compliance with the region-specific recommendations.

Table 1. Sizes of Standard Sieve Series in Range of Interest

Principal sizes	ISO Nominal Aperture		US Sieve No.	Recommended USP Sieves (microns)	European Sieve No.	Japan Sieve No.
	Supplementary sizes					
	R 20/3	R 20 R 40/3				
11.20 mm	11.20 mm 10.00 mm	11.20 mm 9.50 mm			11200	
8.00 mm	9.00 mm 8.00 mm 7.10 mm	8.00 mm 6.70 mm				
5.60 mm	6.30 mm 5.60 mm 5.00 mm	5.60 mm 4.75 mm			5600	3.5
4.00 mm	4.50 mm 4.00 mm 3.55 mm	4.00 mm 3.35 mm	5 6	4000	4000	4.7 5.5
2.80 mm	3.15 mm 2.80 mm 2.50 mm	2.80 mm 2.36 mm	7 8	2800	2800	6.5 7.5
2.00 mm	2.24 mm 2.00 mm 1.80 mm	2.00 mm 1.70 mm	10 12	2000	2000	8.6 10
1.40 mm	1.60 mm 1.40 mm 1.25 mm	1.40 mm 1.18 mm	14 16	1400	1400	12 14
1.00 mm	1.12 mm 1.00 mm 900 µm	1.00 mm 850 µm	18 20	1000	1000	16 18
710 µm	800 µm 710 µm 630 µm	710 µm 600 µm	25 30	710	710	22 26
500 µm	560 µm 500 µm 450 µm	500 µm 425 µm	35 40	500	500	30 36
355 µm	400 µm 355 µm 315 µm	355 µm 300 µm	45 50	355	355	42 50
250 µm	280 µm 250 µm 224 µm	250 µm 212 µm	60 70	250	250	60 70
180 µm	200 µm 180 µm 160 µm	180 µm 150 µm	80 100	180	180	83 100
125 µm	140 µm 125 µm 112 µm	125 µm 106 µm	120 140	125	125	119 140

90 μm	100 μm 90 μm 80 μm	90 μm	170	90	90	166
		75 μm	200			200
63 μm	71 μm 63 μm 56 μm	63 μm	230	63	63	235
		53 μm	270			282
45 μm	50 μm 45 μm 40 μm	45 μm	325	45	45	330
		38 μm			38	391

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61 Use micrometers or millimeters in denoting test sieve aperture size. [NOTE—Sieve numbers are
62 provided in the table for conversion purposes only.]

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64 Test sieves are selected to cover the entire range of particle sizes present in the powder or
65 granule sample. A nest of sieves following a $\sqrt{2}$ progression of the sieve aperture sizes is
66 recommended. The nest is assembled with the coarsest sieve aperture sizes at the top and the finest at
67 the bottom.

68 Test sieves are made from stainless steel or, less preferably, from brass or other suitable non-reactive
69 wire. Sieve frames are in general circular and made of a non-corrosive material. The standard frame
70 size has a diameter of 200 mm or 203 mm (8-inches). Alternatively, a frame size of 75 mm or 76 mm
71 (3-inches) in diameter can be used when sieving smaller quantities than can be accommodated on a
72 200 mm or 203 mm (8-inches) test sieve.

73 Test sieves are carefully examined for gross distortions and fractures, especially at their sieve frame
74 joints, before use.

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76 **Qualification** – Test sieves are qualified in accordance with the specifications of the current edition
77 of ISO 3310 - 1. The test sieves may be qualified optically to estimate the average aperture size, and
78 aperture size variability of the sieve. Alternatively, for the evaluation of the effective aperture size of
79 test sieves, certified reference materials, for example, standard glass spheres in various sizes are
80 available.

81 **Cleaning Test Sieves**—Ideally, test sieves are cleaned using only an air jet or a liquid stream. If
82 some apertures remain blocked, careful gentle brushing may be used as a last resort.

83 **Test Sample**—If the test sample weight is not given in the monograph for a particular material,
84 use a test sample having a weight between 25 g and 100 g, depending on the untapped bulk density
85 of the powder or granule, and test sieves having a diameter of 200 mm or 203 mm (8 inches). For test
86 sieves having a diameter of 75 mm or 76 mm (3 inches) the amount of test sample that can be
87 accommodated is approximately $1/7^{\text{th}}$ of the amount that can be accommodated by a 200 mm or 203
88 mm test sieve. Determine the most appropriate weight for a given powder or granule by test sieving
89 accurately weighed test sample of different weights, such as 25 g, 50 g, and 100 g, for the same time
90 period and the same agitation method. [NOTE—If the test results are similar for the 25 g and 50 g
91 test sample, but the 100 g test sample shows a lower percentage through the finest test sieve, the 100
92 g test sample is too large.] Where only a test sample of 10 g to 25 g is available, smaller diameter
93 test sieves conforming to the same aperture specifications may be substituted, but the endpoint must
94 be re-determined. It may be necessary to use test samples with a lower weight (e.g. down to 5 g). For
95 powders or granules with low untapped bulk density, or for powders or granules mainly comprising
96 particles with a highly isodiametrical shape, test sample weights below 5 g for a 200 mm or 203 mm
97 (8-inches) test sieve may be necessary to avoid excessive blocking of the sieve apertures. During
98 validation of a particular sieve analysis method, it is expected that the problem of sieve aperture
99 blocking will have been addressed.

100 If the powder or granules are prone to gaining or losing significant amounts of water as a result
101 of variations in the humidity conditions, the test must be carried out in an appropriately controlled
102 environment. Similarly, if the powder or granules are prone to cohesion, adhesion or electrostatic

103 charging, careful observation must be made to minimize the risk of such effects biasing the analysis.
 104 A dispersing aid, such as colloidal silicon dioxide and/or aluminum oxide, may be added at a 0.5
 105 percent (m/m) level to minimize these effects. If the above effects cannot be eliminated, consider an
 106 alternative particle-sizing technique.

107 **Agitation Methods**—Several different test sieve and powder agitation devices are
 108 commercially available, all of which may be used to perform sieve analyses. However, the different
 109 methods of agitation may give different results for sieve analyses and endpoint determinations
 110 because of the different types and magnitude of the forces acting on the individual particles under
 111 test. Methods using mechanical agitation or electromagnetic agitation, and that can induce either a
 112 vertical oscillation or a horizontal circular motion or tapping or a combination of both tapping and
 113 horizontal circular motion are available. Other methods such as entrainment of the particles in an air
 114 stream or by using sonication may also be used. The results must indicate which agitation method
 115 was used and the agitation parameters used (if they can be varied), since changes in the agitation
 116 conditions will give different results for the sieve analysis and endpoint determinations and may be
 117 sufficiently different to give a failing result under some circumstances.
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119 **Endpoint Determination**—The sieving analysis is complete when the weight on any of the
 120 test sieves does not change by more than 5% or 0.1 g (10% in the case of 75 mm or 76 mm test
 121 sieves) of the previous weight on that test sieve. If less than 5% of the total test sample weight is
 122 present on a given test sieve, the endpoint for that test sieve is increased to a weight change of not
 123 more than 20% of the previous weight on that test sieve.

124 If more than 50% of the total test sample weight is found on any one test sieve, unless
 125 otherwise indicated in the monograph, the test should be repeated with the addition to the sieve nest
 126 of a coarser test sieve intermediate between that carrying the excessive weight and the next coarsest
 127 test sieve in the original nest, i.e., addition of the ISO series sieve omitted from the nest of sieves.
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129 ANALYTICAL SIEVING METHODS

130 **Sieving by Mechanical Agitation**

131 Tare each test sieve to the nearest 0.1 g. Place an accurately weighed quantity of test
 132 sample on the top (coarsest) test sieve and replace the lid. Agitate the nest of sieves for 5 minutes
 133 then carefully remove each test sieve from the nest without loss of sample. Reweigh each test sieve,
 134 and calculate the weight of sample on each test sieve. Determine the weight of the sample in the
 135 collecting pan in a similar manner. Reassemble the nest of sieves and agitate for 5 minutes. Remove
 136 and weigh each test sieve as previously described. Repeat these steps until the endpoint criteria are
 137 met (see *Endpoint Determination* under *Test Sieves*). Upon completion of the analysis, reconcile the
 138 weights of samples of each sieve fraction and the collecting pan. Total losses must not exceed 5% of
 139 the weight of the original test sample.
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141 Repeat the analysis with a fresh test sample but using the sieving time equal to that of the
 142 combined agitation times used above. Confirm that this sieving time conforms to the requirements
 143 for endpoint determination. When this endpoint has been validated for a specific powder or granules,
 144 then this fixed sieving time may be used for future analyses, providing the particle-size distribution
 145 falls within normal variation.
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147 **Sieving by Air Entrainment Methods**

148 Different types of commercial equipment that use a moving air current are available for
 149 sieving. In air-jet sieving a single test sieve is used at a time. It uses the same general sieving
 150 methodology as that described under the *Sieving by Mechanical Agitation*, but with a standardized
 151 air-jet replacing the mechanical agitation mechanism. It requires sequential analyses on individual
 152 test sieves starting with the finest test sieve to obtain a particle-size distribution. Air-jet sieving often
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154 includes the use of finer test sieves than used in ordinary dry sieving. This technique is more suitable
155 where only some oversize or undersize fractions are needed.

156 In the sonic sifting method, a nest of sieves is used, and the test sample is carried in a vertically
157 oscillating column of air that lifts the powder or the granules and then carries it back against the
158 aperture at a given number of pulses per minute. It may be necessary to lower the test sample amount
159 to 5 g, when sonic sifting is employed.

160 The air-jet sieving and sonic sifting methods may be useful for powders or granules when
161 mechanical sieving techniques are incapable of giving a meaningful analysis.

162 These methods are highly dependent upon proper dispersion of the powder in the air current.
163 This requirement may be hard to achieve if the method is used at the lower end of the sieving range
164 (i.e., below 75 μm), when the particles tend to be more cohesive, and especially if there is any
165 tendency for the sample to develop an electrostatic charge. For the above reasons endpoint
166 determination is particularly critical, and it is very important to confirm that the oversize sample
167 comprises single particles and is not composed of unintended agglomerates or aggregates.

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169 **INTERPRETATION**

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171 The raw data must include the weight of test sample, the total sieving time, the sieving
172 methodology and the set values for any variable parameters, in addition to the weights retained on
173 the individual sieves and in the collecting pan. It may be convenient to convert the raw data into a
174 cumulative weight distribution. If it is desired to express the data in terms of a cumulative weight
175 undersize or oversize distribution, the range of test sieves used should include a test sieve through
176 which all the test sample passes. On the other side it may be difficult to use a test sieve which
177 completely retains all the particles. In this case the lower limit of the finest particle size class may be
178 estimated e.g. by using imaging methods.

179 If there is evidence that unintended agglomerates or aggregates are retained in any sieved sample or
180 are formed during sieving, the use of dry sieving is unlikely to give good reproducibility and a
181 different particle-size analysis method may be considered.