

the proportion of rework allowed and how the calculations will be made to the BOM.

XXXIX. SCALE-UP

Whereas the formulations given in this book are robust enough to be scaled-up to most sizes, manufacturers may find the need to modify these to comply with scaled-up performance. For example, the quantity of lubricants, the amount of moisture, the size of the granules, etc., are all pertinent.

XL. SEGREGATION

Particulate solids, once mixed, have a tendency to segregate by virtue of differences in the shape, size, and density (other variables are also important) of the particles of which they are composed. This process of separation occurs during mixing as well as during subsequent handling of the completed mix. Generally, large differences in particle size, density, or shape within the mixture result in instability in the mixture. The segregation process normally requires energy input and can be reduced following mixing by careful handling. One of the most common reasons for postblending (after adding lubricants) segregation is overblending. Lubricants develop electric charge very quickly, making compression difficult and altering the dissolution profile. A critical specification in the manufacturing method is the length of blending. Follow this strictly.

XLI. SIFTING INGREDIENTS AND GRANULES

Whereas the specifications of starting materials are specified, the powders often form aggregates during storage; a point-of-use check of aggregation is needed. It is a good idea to sift all ingredients through specified sieves before adding them to mixing or blending vessels. For most raw materials, sifting through a #60 sieve (250 μ m) is desired. Know that passing materials through finer sieves can generate electrostatic charges. Wet mass is passed through a #8 (2.38 mm) sieve, and dried granules are passed through a #16 (1.19 mm) mesh sieve. Lubricants should be sieved through a #60 mesh, except for magnesium stearate, which should not be shifted through an opening smaller than that of a #35 mesh. This is necessary to avoid building up electrical charges. A conversion chart for sieve sizes from U.S. Mesh to inches and microns (or millimeters) follows:

U.S. Mesh	Inches	Microns	Millimeters
3	0.2650	6730	6.730
4	0.1870	4760	4.760
5	0.1570	4000	4.000
6	0.1320	3360	3.360
7	0.1110	2830	2.830
8	0.0937	2380	2.380
10	0.0787	2000	2.000
12	0.0661	1680	1.680
14	0.0555	1410	1.410
16	0.0469	1190	1.190
18	0.0394	1000	1.000
20	0.0331	841	0.841
25	0.0280	707	0.707

U.S. Mesh	Inches	Microns	Millimeters
	0.0232	595	0.595
	0.0197	500	0.500
	0.0165	400	0.400
	0.0138	354	0.354
	0.0117	297	0.297
	0.0098	250	0.250
	0.0083	210	0.210
	0.0070	177	0.177
	0.0059	149	0.149
	0.0049	125	0.125
	0.0041	105	0.105
	0.0035	88	0.088
	0.0029	74	0.074
	0.0024	63	0.063
	0.0021	53	0.053
	0.0017	44	0.044
	0.0015	37	0.037

XLII. SPECIFICATIONS

The development of a product and its manufacturing process and specifications, the design of the validation protocol, and the demonstration (validation) runs of the full-scale manufacturing process require scientific judgment based on good scientific data. The in-process control and product specifications are established during the product development process, with the test batch serving as the critical batch used for the establishment of specifications. Specifications, such as hardness and particle size, should be established before validation of the process; these specifications should be included in the validation protocol. The use of product development runs of the process to establish specifications and demonstrate that the system is validated often causes problems.

XLIII. STABILITY TESTING

Even though compressed solids offer a major advantage over other dosage forms in being the most stable, both chemically and physically, complete stability profiles must be developed every time any change, albeit minor, is made in the formulation, the processing conditions, the equipment used, or even the manufacturing site used. This applies not just to drugs with known stability problems, but even to highly stable drugs, such as erythromycin. Subtle alternations in formulation can bring such major unsuspected changes as prolonged disintegration and dissolution. The stability profiles are developed over a span of time to establish not only the chemical stability (providing the labeled quantity), but also the in vitro release characteristics. Stability testing is also required to be conducted in the specific temperature zone areas as dictated by compendia. This creates a significant problem for multinational companies selling products around the world, where different zone temperature stability requirements come into play. A universal formula is often difficult to design for this reason. Generic manufacturers must, therefore, take this aspect into consideration and mimic the formulations used by innovators in the world regions where these products are to be sold. Unfortunately, it is not as easy to obtain this information for formulations sold outside of the United States. Some reverse engineering may be in order to accomplish this.