

granulation studies that would include blend uniformity, sieve analysis, and moisture. In the formulations provided in this book, the in-process milestones are not generally identified; the manufacturer is supposed to know this. Critical in-process testing stages for compressed solids are

- assuring cleanliness of equipment;
- checking and recording temperature where specified for dissolving or mixing ingredients, such as in the making of binder solutions or slurries;
- testing of granules for content uniformity, flow rate, tap density, moisture content (LOD), or other specific testing, as required;
- testing of tablets during compression for weight, thickness, friability, and disintegration;
- final testing of weight, friability, content uniformity, disintegration, and dissolution; and
- assay and finished product release.

With regard to moisture, some tablets set up (harden) upon aging as a result of poor moisture control and inadequate specifications. For example, this was shown to be a major problem with carbamazepine tablets.

XXIX. LOSS ON DRYING

This procedure determines the amount of volatile matter of any kind that is driven off under the conditions specified. Mix and accurately weigh the substance to be tested, and, unless otherwise directed in the individual monograph, conduct the determination on 1 to 2 g. If the test specimen is in the form of large crystals, reduce the particle size to about 2 mm by quickly crushing. Take a glass-stoppered, shallow weighing bottle that has been dried for 30 minutes under the same conditions to be employed in the determination. Put the test specimen in the bottle, replace the cover, and accurately weigh the bottle and the contents. By gentle, side-wise shaking distribute the test specimen as evenly as practicable to a depth of about 5 mm and not more than 10 mm in the case of bulky materials. Place the loaded bottle in the drying chamber, remove the stopper, and leave it in the chamber. Dry the test specimen at the temperature and for the time specified in the monograph. (*Note:* The temperature specified in the monograph is to be regarded as being within the range of $\pm 2^\circ\text{C}$ of the stated Figure.) Upon opening the chamber, close the bottle promptly, and allow it to come to room temperature in a desiccator before weighing.

If the substance melts at a lower temperature than that specified for the determination of LOD, maintain the bottle with its contents for 1 to 2 hours at a temperature 5°C to 10°C below the melting temperature, then dry at the specified temperature. Where the specimen under test is a tablet, use powder from not less than four tablets ground to a fine powder. Where the individual monograph directs that the LOD should be determined by thermogravimetric analysis, a sensitive electrobalance must be used. Where drying in vacuum over a desiccant is directed in the individual monograph, a vacuum desiccator or a vacuum drying pistol, or other suitable vacuum drying apparatus must be used. When drying in a desiccator is specified, exercise particular care to ensure that the desiccant is kept fully effective by frequently replacing. Where drying in a capillary-stoppered bottle in vacuum is directed in the individual monograph, use a bottle or tube fitted with a stopper having a 225 ± 25 mm diameter capillary, and maintain the heating chamber at a pressure of 5 mm

or less of mercury. At the end of the heating period, admit dry air to the heating chamber, remove the bottle, and with the capillary stopper still in place, allow it to cool in a desiccator before weighing.

Many pharmacopoeial articles are hydrates or contain water in adsorbed form. As a result, the determination of the water content is important in demonstrating compliance with the pharmacopoeial standards. Generally, one of the methods given next is called for in the individual monograph, depending upon the nature of the article. In rare cases, a choice is allowed between two methods. When the article contains water of hydration, method I (titrimetric), method II (azeotropic), or method III (gravimetric) is employed, as directed in the individual monograph.

XXX. MANUFACTURING YIELDS

The formulas provided here include scale as well as quantities for 1000 tablets; often in a scale-up, yields must be calculated to extrapolate exact quantities needed for a specific batch size; yields vary because of differences in the tablet weight (within the specified range), losses in equipment, and losses to the environment. The exhaust or vacuum can carry with it a lot of product at times.

XXXI. MASTER FORMULA

This document must include specific manufacturing directions for the full-scale commercial process, including in-process and finished product specifications. The cGMP-compliant master formula will have room for direct entry onto the documents of all critical parameters, such as temperature, mixing times, LOD, etc., beside signatures of the persons responsible for complying with the specifications. No specific guidelines are provided for the formatting of this document. However, those skilled in assuring compliance with the GMP know the art of capturing most eventualities that may arise in the manufacturing of the product. The key is to assure that no individual discretions are allowed.

XXXII. MULTIPLE-ITEM ENTRIES

In the formulations provided in this book, an ingredient may appear in multiple places; this is necessary so as to identify the different quantities used at different stages and at different times for different purposes. For example, the dry form of starch may be mixed with the drug and then used in the making of a paste for granulation. Similarly, solvents are often listed in many places.

XXXIII. MULTIPLE STRENGTHS OF FORMULATIONS

The formulations disclosed in this book handle multiple strengths in two ways: one to adjust the fill weight of tablets and the other to provide a different formulation. There are specific reasons for this. Where the quantity of API is high, a simple doubling of fill weight might not work, and an adjustment to the excipients will be required. On the other hand are products where the API is less than 1% of the total weight, in which case, the formulation remains the same, with one of the