Common tablet fillers include lactose, starch, dibasic calcium phosphate, and microcrystalline cellulose. Chewable tablets often contain sucrose, mannitol, or sorbitol as fillers. Where the amount of active ingredient is small, the overall tableting properties are, in large measure, determined by the filler. Because of problems encountered with the bioavailability of hydrophobic drugs of low water solubility, water-soluble diluents are used as fillers for these tablets. Binders give adhesiveness to the powder during the preliminary granulation and to the compressed tablet. They add to the cohesive strength already available in the diluent. While binders may be added dry, they are more effective when added out of solution. Common binders include acacia, gelatin, sucrose, povidone, methylcellulose, carboxymethylcellulose, and hydrolyzed starch pastes. The most effective dry binder is microcrystalline cellulose, which is commonly used for this purpose in tablets prepared by direct compression. A disintegrating agent serves to assist in the fragmentation of the tablet after administration. The most widely used tablet disintegrating agent is starch. Chemically modified starches and cellulose, alginic acid, microcrystalline cellulose, and crosslinked povidone are also used for this purpose. Effervescent mixtures are used in soluble tablet systems as disintegrating agents. The concentration of the disintegrating agent, method of addition, and degree of compaction play roles in effectiveness. Lubricants reduce friction during the compression and ejection cycles. In addition, they aid in preventing adherence of tablet material to the dies and punches. Metallic stearates, stearic acid, hydrogenated vegetable oils, and talc are used as lubricants. Because of the nature of this function, most lubricants are hydrophobic, and as such, tend to reduce the rates of tablet disintegration and dissolution. Consequently, excessive concentrations of lubricant should be avoided. PEGs and some lauryl sulfate salts have been used as soluble lubricants, but such agents generally do not possess optimal lubricating properties, and comparatively high concentrations are usually required. Glidants are agents that improve powder fluidity, and they are commonly employed in direct compression where no granulation step is involved. The most effective glidants are the colloidal pyrogenic silicas. Colorants are often added to tablet formulations for aesthetic value or for product identification. Both D&C and FD&C dyes and lakes are used. Most dyes are photosensitive, and they fade when exposed to light. The U.S. FDA regulates the colorants employed in drugs.

XLVIII. WATER-PURIFIED USP

As a general practice, the water used in wet granulation processes should be of at least the water-purified USP grade. Other grades are acceptable, provided their use can be validated, mainly for the reasons of microbiological quality and the presence of other dissolved solids.

XLIX. WEIGHT VARIATION AND CONTENT UNIFORMITY

Tablets are required to meet a weight variation test, where the active ingredient comprises a major portion of the tablet and where control of weight may be presumed to be an adequate control of drug content uniformity. Weight variation is not an adequate indication of content uniformity, where the drug substance comprises a relatively minor portion of the tablet, or where the tablet is sugar coated. Thus, the pharmacopoeia generally requires that coated tablets and tablets containing 50 mg or less of active ingredient, comprising less than 50% by weight of the dosage-form unit, pass a content uniformity test, wherein individual tablets are assayed for actual drug content.

L. WET GRANULATION VS. DRY GRANULATION OR DIRECT COMPRESSION

Drug powders are often not easily compressible. Even if they are compressible, the small quantity that needs to be dispensed requires the adding of excipients for bulking the product; however, the addition of these compatible bulking agents may render the mixture less compressible. Books were written on the physics of powder compression. In a nutshell, the compression of powders involves the breaking of a crystal lattice and the rebonding of lattices to yield a unit structure. Binders provide the bridging gap between and among the ingredients that would rather stay away (to put it simply). With compression machines, the requirement that powders fill the compression cavities as they are compressed no longer holds. The conundrum with powders is that they must flow easily to fill the cavities, but as the particle size gets smaller, the specific surface area increases, along with interparticulate friction that keeps the powder from flowing (angle of repose), subject to the individual characteristics of the chemical. Therefore, for the powders to easily flow into compression cavities, they must be present in granular form, rather than in the form of fine powder. Powders can be converted to granular form by wetting them and drying to form the bonds between particles, particularly in the presence of binding agents (the most popular being starch). The wet granulation process, therefore, involves mixing the powders with a paste of starch (generally approximately 30%) or using polyvinylpyrrolidone (PVP) in an organic solvent to make a wet mass. In most instances, the characteristic of the wet mass is judged by how well it forms a mass as tested. The wet mass is then passed through a coarse mesh, spread on trays, and dried at 50°C to 60°C or directly placed in a fluid-bed dryer. The test of drying is that the LOD ranges from 1% to 3%. This is referred to as wet granulation. Dry granulation is a process where the active drug is mixed with ingredients that are inherently granular and compressible or are made by modifications through wet granulation, to impart good flow ability and compressibility to the mix. Several APIs are also available in direct compressible grades, often coated to impart an additional element of chemical stability. Directly compressible aspirin or ascorbic acid are good examples. The cost of APIs rendered compressible is obviously higher; however, in the long run, it is cheaper to use directly compressible powders.

LI. MULTIVARIATE METHODS IN TABLET FORMULATION

The discussion presented demonstrates that a large number of formulation variables inevitably come into play when formulating a solid dosage form; whereas, each dosage form has its own focus on overcoming inherent difficulties, the release from solid dosage forms and their desirability makes them most widely studied. Drugs are mostly administered in formulated forms and tablets account for more than 80% of all pharmaceutical dosage forms administered. The need to prepare an easily administered dose by mouth or other body cavities in a stable form and one that releases the drug on a