partially dissolve and recrystallize upon drying as a different physical form.

An intensifier bar in the center of the blender, which rotates at very high speeds, breaks down smaller and harder agglomerates. A major disadvantage of this type of blender is that the extremely high speed of the intensifier bar generates considerable heat that can sometimes result in the charring of some sugar-base granulations. It should be pointed out that these same comments are applicable to other high-energy mixers, which also rely on high-speed choppers to disperse powders. Also, between-product cleaning of the blender requires disassembly of the intensifier bar.

5. Plastic Bag

Any discussion of mixers would not be complete without addressing the plastic bag. Manufacturers resorted to the blending or manufacture of a trituration in a plastic bag. Obviously, it is difficult to reproduce such a process, and there is the potential for loss of powder as a result of breakage or handling. When the plastic bag has been used, directions are usually not specific, and one would not know by reading the directions that a plastic bag was employed. The use of a plastic bag cannot be justified in the manufacture of a pharmaceutical product. In fact, it continues to be a popular method, as often mentioned in the formulations described in this treatise.

B. Dryers

Two basic types of dryers are used. One is the oven dryer, where the wet granulation is spread on trays and dried in an oven. The second dryer is the fluid-bed dryer, in which the wet granulation is "fluidized" or suspended in air. A third type recently introduced involves drying of granulations in vacuo while being mixed and processed. Generally, the fluid-bed dryer yields a more uniform granulation with spherical particles. However, this may result in compression problems that may require additional compression force to remedy these problems. It is not unusual to see manufacturers change from an oven dryer to a fluid-bed dryer. However, such a change should be validated for equivalency with conducted in vitro esting, such as hardness, disintegration, and comparative dissolution, and stability testing. Major changes in process details will require demonstration of bioequivalence.

Other issues of concern with drying include moisture uniformity and cross-contamination. Tray dryers present more moisture uniformity problems than fluid-bed dryers. Obviously, a dryer should be qualified for heat uniformity and a program developed to assure moisture uniformity in granulations at the end point of drying. With respect to fluid-bed dryers, moisture problems can occur if the granulation is not completely fluidized.

Regarding cross-contamination, oven dryers, particularly those in which air is recirculated, present cross-contamination problems because air recirculates through a common filter and duct. For fluid-bed dryers, the bag filters present cross-contamination problems. To minimize problems, manufacturers should use product-dedicated bags.

C. Tablet Compression Equipment

Another important variable in the manufacturing process is the tablet press or encapsulating machine. The newer dosage form equipment requires granulations with good flow characteristics and good uniformity. The newer tablet presses control weight variation by compression force and require uniform granulation to function correctly. Setup of the microprocessor-controlled tablet press usually includes some type of challenge to the system. For example, a short punch is sometimes placed among the other punches. If the press is operating correctly, it will sound an alarm when a lower- or higher-weight tablet is compressed.

Different tablet compression equipment can cause dose uniformity, weight uniformity, and hardness problems. For example, vibrations during tablet compression can cause segregation of the granulation in the feed hopper. The speed of the machine can affect fill of the die and tablet weight. Therefore, as previously discussed, it is important to have specific operating directions.

Many unit operations now provide for blending in totes, with discharge of the tote directly into tablet compression equipment. Because of segregation problems at the end of discharge, tablets from the end of compression should be tested for content uniformity. The use of inserts in totes was shown to minimize segregation.

With regard to the newer computer-controlled tablet compression equipment, buckets of tablets are often rejected because of potential weight variation problems. The disposition of these tablets, as well as the granulation and tablets used to set up the press, should be in accordance with written methods. Reworking processes for culls must be validated.

With regard to encapsulation operations, the hygroscopic nature of gelatin capsules and some of the granulations requires humidity controls for storage of the empty capsules and their subsequent filling. Scale-up of capsule products also presented some problems because of the different types of encapsulation equipment. Older equipment that operated on gravity fill, such as the Lilly and Parke-Davis machines, was commonly used for manufacturing capsules in clinical manufacturing areas. When formulations were scaled up to high-speed encapsulation equipment, flow problems and poor weight variation resulted. Additionally, some of the newer equipment provides for the formation of a slug, which could impact dissolution.

D. Coating Equipment

Many tablets are now coated with an aqueous film coat that is usually very soluble. Current technology provides for fixed sprays of the coating solution. The volume of coating solution, rate, and temperature can be controlled by some of the more highly automated operations. However, for many sugar-coated, enteric-coated, and delayed-release products, some portions of the coating process are not highly soluble and are performed manually. Generally, the shellac undercoat used for sugar-coated tablets presented disintegration and dissolution problems, particularly in aged samples.

With respect to poor disintegration, ferrous sulfate tablets probably represent the classical example. Over the years, there have been many recalls from many different manufacturers for poor disintegration of coated ferrous sulfate tablets. Likewise, there have been many problems with poor dissolution attributed to the coating process. Again, the shellac undercoat hardens, and even sometimes cracks, resulting in poor dissolution.

The numbers of applications of coats, volume of coating solution in a specific application, and temperature of the solution during applications are parameters that need to be addressed. For example, the temperature of the application and even heat during drying can cause dissolution failures in aged tablets. Another problem associated with the coating process concerns the heat applied to products that are sensitive to heat. For example, it was shown that estrogen tablets are heat sensitive and exhibited stability problems. Thus, it is important to control this phase of the process.