

major components, such as lactose or dicalcium phosphate, providing compensation for the additional weight. Then, the tablet can be compressed at the same weight.

#### XXXIV. NOVEL DRUG DELIVERY SYSTEMS

From osmotically driven release of the API to wax matrices to plastic “ghosts” (e.g., Gradumet<sup>®</sup>), the compressed solid dosage forms offer a variety of possibilities for incorporating novel drug delivery systems. It should be noted that the compression force required to manufacture the dosage form can deform a structured component; on the other hand, the high compression force and the resultant rise in temperature that is inevitable can be used to create unique dosage form designs. One such example is the use of PEG 6000 or 8000 in direct compression formulations. The compression pressures in a typical tableting machine or in a roller compactor are generally high enough to produce sufficient heat to melt the PEGs and then congeal to provide adequate binding without the need for wet massing. The author used this technique to formulate a myriad of drugs, particularly those subject to stability problems, such as vitamins. PEGs are compatible with most drugs, are cheap, and dissolve rapidly to release the drug. The author highly recommends using this technique to formulate directly compressible formulations instead of using the direct-compression-grade raw materials that are very expensive. Another technique that lends itself appropriately to solid compression is the use of solid solutions. Many drugs, when melted with water-soluble compounds, such as succinic acid, PEG, etc., congeal in a molecular dispersion, which, when placed in the gastrointestinal environment, releases the drug rapidly—it is already in a solution state. Wax embedding is another process (such as used for diltiazem) for moderating the release of drugs.

Briefly, the formulator has many tools available with which to formulate novel drug delivery systems with compression of solids. These techniques have, however, not been exploited as widely as their potential offers. The young formulators not yet biased by the need to follow a traditional route of formulating are encouraged to experiment with a myriad of possibilities, using components that have well proven their utility but in a different role. Remember, a temperature rise during the compression process is a source of energy that can be put to use.

#### XXXV. PARTICLE COATING

Even though solid-state compression excludes moisture, which is the primary starting point in chemical degradation, these dosage forms are not impervious to atmosphere; this protection is generally provided by coating the final compressed dosage form, such as by sealing with waxes. However, there are instances where it may be necessary to coat the particles of the drug before incorporating them into formulations. There can be several reasons for doing this, besides imparting greater stability. It is done to mask the taste, for example, in chewable tablets, to improve flow in tablets comprising a larger proportion of the active drug, to impart specific release characteristics, or to protect the gastrointestinal mucosa (such as in the case of particle-coated iron tablets). Coated particles should be treated as a specialized form of excipient, which must be properly tested for its specifications

prior to incorporating in the final dosage form. Most of the particle-coating methods involve a fluid-bed system or coating on a nonpareil bead.

#### XXXVI. PRESERVATIVES IN COMPRESSED SOLID DOSAGE FORMULATIONS

As a rule of thumb, good formulations include only essential components. Because compressed solids have low moisture content, microbiological stability generally does not pose a problem, with few exceptions. However, in the wet granulation process, slurries or pastes are made that are water-based and are often kept for a few hours before being used, requiring the use of preservatives, particularly when gelatin is also used with starch. Generally, a standard combination of propylparabens and methylparabens would do. Preservatives are also included in compressed solids, where the compositions may be highly hygroscopic, resulting in localized liquefaction of powders that might promote microbial growth.

#### XXXVII. PUNCH SIZE AND SHAPE

The choice of punch size is dependent on the amount of API, the quantity of excipients needed to make it compressible, and what can be reasonably administered. Tablets ranging in weight from less than 100 mg to over 1 g are compressed in 6- to 15-mm-diameter punches. The size is also important because a proportion between thickness and diameter must be maintained. Thick tablets are difficult to eject from dies, such as a long cylindrical product. Experienced machine operators know how well a tableting mix compresses on one punch size and shape, and it becomes difficult to compress using other shapes and sizes. Whereas round tablets are the easiest to compress (from a technical viewpoint of design of punches to ejection), manufacturers use all different shapes, from bugs bunny-shaped vitamins to diamond-shaped Viagra<sup>®</sup> tablets.

The formulations provided in this book may have to be altered to meet the compaction requirements of different punch shapes and sizes other than those recommended here. Concave punches (giving convex tablets) are made to reduce the contact of compressed material with the wall of the die. This makes ejection of a tablet easier. However, because of the shape, there may be more picking of tablets. In several formulations described here, biplanar flat, round punches are recommended. The identification marks or logos on the tablets create additional problems in the picking of tablets. The polishing of punches remains an essential part of good tablet compressing. Often, punches wear out fast depending on the type of compression material used.

Regardless of what the supplier of a punch recommends, a punch must be replaced once it fails to provide the surface quality needed. Punches should ideally be replaced in groups and not individually (except to replace broken items).

#### XXXVIII. REWORKING CULLS

During the setup of machines and through rejection, especially in automated rejection systems, there may be a substantial amount of culls available. In most instances, it would be prudent to just discard them; however, for expensive APIs, reworking can be done. An internal SOP should clearly define