One of the solvents commonly used as a pharmaceutical aid for dissolution of hydrophobic drugs is ethanol. However, for drugs to be used in soft gelatin capsules, ethanol cannot be used easily because ethanol diffuses quite readily through soft gelatin films (Moreton and Armstrong, 1995) at a fairly rapid rate. The diffusion is fast enough that most of the ethanol would diffuse out through the drying phase during the manufacture of softgel capsules. Moreton and Armstrong (1998) found that changing the composition of plasticized gelatin gels changes the diffusion coefficient of the gelatin film to ethanol. They showed that replacing glycerol with higher polyols (xylitol or sorbitol) results in substantial reduction in the diffusion coefficient of ethanol. The greatest reduction, 5- to 10-fold, was observed in films with the least amount of moisture.

The compounds that are difficult to formulate in soft gelatin capsules are fairly water-soluble small organic molecules, acids, and bases. These compounds tend to cause migration of water from the shell into the cavity and tend to permeate into the capsule shell, depending on the water content of the shell. Armstrong et al. (1984) studied the aqueous solubility of four different solutes and their relative migration into the capsule shell from an isopropyl myristate formulation. They concluded that with an increase in the aqueous solubility, the fraction of active drug migrating into the capsule shell increased as well. In the case of acids and bases, Patel et al. (1989a, 1989b, 1992) showed that it is possible to neutralize them using a corresponding base or acid. The resulting salt or ester may then be formulated in a hydrophilic solvent such as polyethylene glycol.

In all of the preceding cases, it is apparent that one has to be aware of the dynamic equilibrium that exists between the soft gelatin capsule contents and the capsule shell during the manufacturing process of soft gelatin capsules (e.g., in the drying of capsules) and long-term storage. It is possible for the contents of the formulation to migrate into the shell, and/or water may permeate from the capsule shell into the capsule cavity.

In addition, one may consider the addition of an antioxidant since soft gelatin capsule shell is permeable to oxygen, resulting in oxidation of oxygen-sensitive, active drug substance. However, the oxidation potential should be confirmed in the preformulation *workup* of the molecule. In a study conducted to evaluate the effects of various formulation and environmental parameters on the oxygen permeability of gelatin film, Hom et al. (1975) concluded that relative humidity and plasticizer concentration affect oxygen permeability the most. The oxygen permeability of the gelatin film made with 40%–50% glycerin increased with increasing relative humidity. The oxygen permeability increased 10-fold by raising the relative humidity from 47% to 80% at room temperature. In general, therefore, it is recommended that soft gelatin capsules be stored in a cool, dry place for maximum stability.

CONTROL AND TESTING

Quality control of the in-process and final product is critical for the overall presentation of any dosage form, and production of soft gelatin capsules is no exception.

In-Process Controls

Some of the in-process controls such as seal tests, shell-thickness checks, fill weights, and shell weights are done during the encapsulation process to decide the fate of the batch and the possibility of taking any corrective action (Stanley, 1986). Weight variation, determination of the content weight (by difference of the gross weight and the weight of the shell), and shell-thickness measurement are among the principal in-process tests.

Batch-Release Tests

The quality control release testing of the batch can be divided into physical, chemical, and microbiological tests. Obviously, some of these tests are product specific, such as chemical tests; however, a few tests are performed owing to the nature of the dosage form, for example, microbiological testing of soft gelatin capsule shells. The description of some of these tests is included for information