(Bicota™, Manisty). The machines used to make them are, however, slow. If a layer separation is necessary (and effective), then it is most often accomplished by triple-layer tablets. It should noted that these techniques are ineffective in the case of reactions that occur via the gas phase. (These types of reactions will be discussed in the following.)

As mentioned, coating is a special case of pocketing. Ferrous fumarate is sometimes coated, but the most famous case of coating is undoubtedly that of vitamin A esters. Prior to this technique, in the early 1950s vitamin A was added, with an antioxidant, to powder blends that were then encapsulated or tableted. The loss of the vitamin was excessive (frequently 50% in 6 months, plus a processing loss). In the early 1950s Hoffmann-La Roche and Pfizer (almost simultaneously) marketed a so-called beadlet. The coating of vitamin A was a bit different from that of other compounds, since the most common ester (acetate) is a liquid. The coating was therefore done by making an emulsion of the vitamin A in a solution of gelatin, spraying this onto an insoluble starch derivative (which rapidly absorbed moisture), and then further drying the beadlet. After drying, the starch derivative could be separate from the vitamin A by sieving. Later, the coated palmitate bead was introduced, and, with normal precautions, oxidation of the vitamin A (except for the droplets on or rather in the surface) was prevented. It follows from this that the finer the beadlet, the less stable will it be (because there will be more surface droplet of vitamin A). 40 mesh is about the coarsest than can be handled in tableting or encapsulation, and this mesh cut offers a good stability. Obviously compression will cause fracture of the beads to some extent and this is the actual stability problem in a dry tablet.

If moisture is present in the tablet, then the gelatin will soften and become more oxygen-permeable, and the stability will suffer. It is therefore always best to perform moisture stress tests in stability programs. At a point in development where enough tablets are available the following is done: four times the regular sample is taken, and this sample is subdivided into four equal portions, A, B, C, and D. A is placed on stability as is. B is exposed to water vapor in a desiccator, and removed and placed on stability when it has gained 0.5% in weight. (The tablets can be placed on Petri dished and weighed periodically.) The procedure is repeated with C to 1% and D to 2%. The information gained is valuable, because it aids in decisions of the following kind: (a) Should a desiccator bag be used? (b) What should the moisture specification on the product be? (c) If there is no effect of moisture, there would be less of a problem selecting plastic bottles for the product.

10. pH OF THE MICROENVIRONMENT

In the strictest sense, the term pH is not defined in a solid system. For it to have meaning, there must be some water mediation; tocopheryl acetate and calcium pantothenate are cases in point. The former is sensitive to high pH, the former to low pH. Calcium pantothenate is frequently admixed with magnesium oxide and granulated separately from the remaining ingredients. In this manner an alkaline microenvironment is created, which ascertains the stability of the vitamin.

In the case of tocopheryl acetate, the hydrolysis is accelerated by hydroxyl ions. Again it is noted that the reaction must be associated with some dissolution step in small amounts of water. The produced tocopherol is much less stable, and hence the hydrolysis and the presence of water are contraindicated. This is a particular