tial potency variation could lead to sub- or supratherapeutic blood levels and perhaps the need to retitrate the patient.

Third, and perhaps most important, there is a perception in some quarters that use of a stability overage is a cop-out that represents an easy Band-Aid approach to formulation that is quite unacceptable in modern pharmaceutical technology. It is thought that a more thorough investigation of the problem and a willingness to devote appropriate resources of time, personnel, and money might well allow the problem to be solved by other, more conventional, formulation approaches that do not require a stability overage.

Formulation approaches to reduce the problem of hydrolysis of drugs in solution have generally been of rather limited success. Recently, complexation of drugs with cyclodextrins has attracted considerable interest (15). Such complexes may show improved resistance to hydrolysis, faster dissolution, and better bioavailability. Of course, since most hydrolysis reactions are catalyzed by hydronium and hydroxyl ions, pH control might appear to have great value as a formulation approach to reducing hydrolysis. In practice, however, this approach has had rather limited success. For drugs liable to hydrolysis that are formulated into tablets, the use of a coating may be of value in improving stability.

In contract to hydrolysis, degradation by oxidation can often be successfully controlled by formulation approaches. There is a range of chelating agents and both oil- and water-soluble antioxidants that are used in products in various parts of the world. When a product contains an antioxidant, it is normal to monitor the amount (or concentration) of antioxidant as part of stability studies. In theory, it would be acceptable if all the antioxidant were used by the end of the shelf life period. In practice, most of us would feel rather uncomfortable if we did not have, say, 25% remaining at the end of the shelf life.

Antimicrobial preservatives, such as sodium benzoate, are commonly added to many pharmaceutical products. The amount (or concentration) of such components should be monitored during stability studies. Although chemical assay for antimicrobial preservatives may be acceptable at most time points, the testing performed at the last time point should be by a microbiological challenge test, such as that specified in the USP.

Perhaps the area where formulation approaches are particularly important in controlling stability problems is the field of protein drugs, an area of ever-increasing importance. Dr. Kottke and Dr. DiBiase give this topic specific attention in their chapter in this book.

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