STABILITY OF PHARMACEUTICAL PRODUCTS

Jagdish Singh.*

Although the pharmaceutical industry has long been aware of the importance of stability testing in product development. it has only been within a few years that major strides have been made in this area. During this period, the empirical approach to stability testing, for the most part, has been replaced by scientific considerations employing certain basic physical-chemical principles.

The stability of pharmaceutical product can be defined in terms of the time period, within which its chemical or biological aciivity is maintained at a predetermined level of labelled potency and its physical characteristics have not changed appreciably. The time is generally counted from the date of manufacture of the product.

The stability may also be defined as the capability of a particular formulation in a specific container to remain within its physical, chemical, therapeutic and toxicological specifications[1].

There are legal, moral, economic and competitive reasons, as well as those of safety and efficacy to monitor, predict and evaluate drug product stability[2]. However, stability may mean different things to different people or to the same people at different times, even those in the pharmaceutical profession. Although unified nomenclature has been proposed, various terminology is still employed to encompass the what and how and why of stability; stability study, kinetic study, compatibility study, stability evaluation, stability-indicating assay, expiration dating, outdating, shelf-life storage legend, preformulation studies, failures of a batch to meet specifications, microbiological stability, stability of the active ingredient, stability of the formulation, stability of the marketed package, stabilty in dispensing package and stability in the hands of the consumer. All of these areas have been referred to stability.

The knowledge of the physico-chemical properties of the drug is equally important to the development pharmacist in efforts to achieve the optimum drug formulation.

Storage Conditions

One aspect of stability evaluation is the determination of the effects of environmental conditions on the product. The factors most commonly tested are heat, humidity, light and air. Temperature tends to accelearte all reactions according to rate theory and the other factors accelerate, catalyze, or mediate hydrolytic, photolytic, oxidative etc. reactions.

These data also form the basis for establishment of an expiration date. Expiration dates, however, have real significance only when they can be related to specific storage con-

* *Department of Pharmaceutics. B. H. U.*

ditions. That a label bears a 5-year expiration date does not mean that the product will be suitable after storage for 5 years under any condition. Packages can provide a degree of protection from some of the elements, but it is still advisable to relate the expiration date to specific storage conditions.

Kiger[3,4] and Schumacher[5] discussed the results of environmental factor on the stability of drugs and listed the storage requirements of some prime drug products for maximum efficiency and the most reliable storage time.

Predictive (Accelerated Testing)

To determine the stability of pharmaceutical product, samples are stored under the anticipated marketed storage conditions, usually ambient temperature and either the content of intact drug or the content of degradation product is monitored by specific analytical, microbiological, or physical methods at predetermined intervals. The point at which the product degrades to the lower limit of its specifications is considered the *shelf-life* Depending on the stability of item, the time involved for this test could be very short or quite long. Obviously, it would be to the investigator's advantage to be able, in a relatively short time, to predict the shelf-life of the product.

Acceleration of chemical decomposition is achieved by raising the temperature of the preparations. Application of the principles of chemical kinetics to the results of accelerated storage tests caried out at three or more elevated temperatures enables prediction to be made of the effective life of the preparation at normal temperatures. The order of reaction for the decomposition proccess is determined by plotting the appropriate function of concentration against time and obtaining a linear relationship. The Arrhenius relationship, given below, is then employed to determine the reaction velocity constant for decomposition at room temperature.

$$K = A_e^{-E/RT}$$

where K is reaction velocity constant.

A is constant which is termed the frequency factor

E is the energy of activation which molecules must possess before they will interact

T is the absolute temp erature.

R is the gas constant

K is obtained from the linear plot of the logarithms of the determined reaction velocity constants against the reciprocals of absolute temperatures, which is exptrapolated to room temperature. 25.°C. The value of k at 25°C may then be substituted in the appropriate rate equation, and an estimate obtained of the time during which the product will maintain the required quality or potency (shelf-life). Formulated drug affected by tropical con-

ditions, mostly tablets and capsules are stored in artificial atmospheres at controlled humidity and temperature.

Accelerated tests for photochemical stability induce rapid decomposition by means of an intense artificial light source simulating the effects of sunlight and room illumination. The relationship between the intensity of light and the rate of photodegradation is a unique function of the product formulation. The quality of light absorbed by the drug sample is determined by measuring the difference in the intensity and quality of light incident upon and transmitted by the product. Price and Osborne (1964) designed an instrument which provides radiant energy of the required wavelength and of sufficient intensity to make such studies possible.

In case of accelerated tests for physical stability, it is not possible to devise a single universal test that will accelerate the breakdown of all preparations. A high degree of stress is applied and it is assumed that the product is stable on normal storage if it withstands the stress.

Finally, the stability of this resultant product in various channels of commerce is of concern to the marketing and distribution departments and to the physician, pharmacist and patient. This concern is manifested by the use of storage legends, expiration dates, protective packaging and dispensing directions. Furthermore from a regulatory view point one should assure that the product is of the "quality, strength, purity, and identity" that it is purported to be throughout the time it is held or offered for sale.

References

1. Remington's Pharmaceutical Sciences, 15th ed, (1975). Hoover, J. E., Ed. Mack publishing Co. Easton.
2. Garrett, E.R., in "Advances in pharmaceutical Sciences", (1967). Vol. 2, Bean, H.S., Beckett, A.H. and Carless, J.E., Eds. Academic, New York, N.Y., 2.
3. Kiger, J.L., Rev. Port. Farm., (1973). **23**, 271.
4. Kiger, J.L., Rev. Int. Serv. Sante Armess terra, mer Air, (1976). **47**, 707. Through Chem. Abstr., (1974). **81**, 96343k.
5. Schumaeher, P. Pharm. Ztg., (1974.) **119**, 321. Through Chem. Abstr. (1974). **81**, 96343k.
6. Bentley's Text Book of Pharmaceutics, 8th edition, 140—168.