CHEMICAL STABILITY OF PHARMACEUTICALS

A HANDBOOK FOR PHARMACISTS

KENNETH A. CONNORS
School of Pharmacy, The University of Wisconsin

GORDON L. AMIDON
School of Pharmacy, The University of Wisconsin

LLOYD KENNON
Formerly School of Pharmacy,
The University of Wisconsin

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CHAPTER 5

Oxidation

On and within a few miles of the earth's surface, oxygen is the most abundant of elements. It makes up about 46% of the earth's crust and, of course, 89% of the water and over 20% of the air. It is the last component that causes many of our pharmaceutical problems. With so much oxygen around, it is no wonder that oxidation reactions, both completed and potential, are omnipresent. Ironically, virtually all of our useful drugs exist in a reduced, not their most oxidized, form; it is clear, then, that "the battle is on."

Whereas in hydrolytic reactions temperature, pH, and the presence of water are the major factors that influence drug decomposition, oxidative reactions are strongly influenced by environmental factors such as light and metal ions, in addition to, of course, oxygen and oxidizing agents. For example, 0.0002 M copper has been shown to increase the rate of ascorbic acid oxidation by a factor of 10,000 over that in the absence of copper. One of the major problems encountered in dealing with oxidation reactions is that some reactants such as oxygen or metal ion need not be present in more than trace quantities to produce significant stability problems. Another interesting aspect of oxidative decomposition is the tendency of many drugs to form colored products and various other formulation components to produce off-odors. Consequently, although only a very low level of oxidative degradation may have occurred, with drug decomposition being insignificant both chemically and therapeutically, the drug product may nevertheless be rejected and not used. Finally, note that oxidation can occur in both aqueous and non-aqueous solutions as well as in the solid state to some extent.

A. NATURE OF OXIDATION

When one considers oxidation, it is important to stability problems will arise from light of the shorter wavelengths, in particular from the short visible and the UV.

When electromagnetic radiation is absorbed, essentially only one of four events occurs:

1. The absorbing molecule decomposes.

2. The energy is either retained until it can be used chemically or is transferred to another molecule, which may or may not decompose.

3. The energy is converted to heat, and no reaction ensues.

4. The absorbing molecule emits light of a different wavelength (fluorescence or phosphorescence), and no decomposition occurs.

The work to be described now illustrates by means of a specific example the very marked, explicit effect of UV light on an oxidative reaction. Solutions (5%) of two therapeutically useful phenothiazine salts, chlorpromazine hydrochloride and prochlorperazine ethanedisulfonate, were placed in a Warburg respirometer to permit measurement of oxygen uptake and were then exposed to a sunlamp. [The structure of chlorpromazine is given in Eq. (5.21); prochlorperazine is similar, with the dimethylamino group being replaced by 4-methyl-1-piperazinyl.] The solutions became colored shortly after the light was turned on, and they continued to darken. The data (1) are shown graphically in Figure 5.1.

C. INHIBITION OF OXIDATION

1. Protection from Light

As previously described, many compounds undergo changes on receiving and absorbing radiant energy (light). When one is dealing with pharmaceutical products, any alterations, light-induced or otherwise, that result in losses in potency or in color or taste changes are detrimental. Therefore, the choice of a suitable container is very important. At the outset of this discussion it is stressed that whatever container

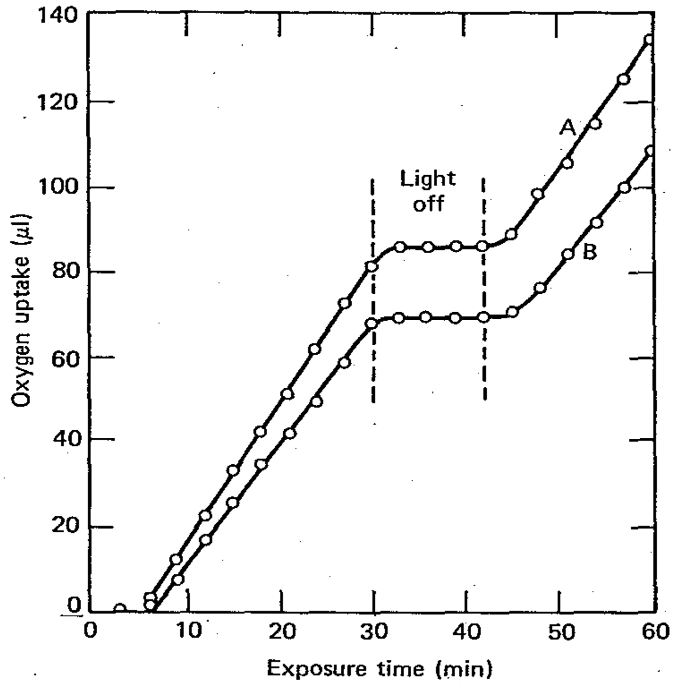

FIGURE 5.1. Plot of oxygen-uptake data for chlorpromazine hydrochloride (A) and prochlorperazine ethanedisulfonate (B) illustrating induction period, the linearity of the uptake with time, and the extreme light dependence of the oxidative degradation (1).

is chosen, it must be tested with the formula it is to hold to ascertain the overall stability characteristics. Although most such testing is done in industrial laboratories, and although the community pharmacist certainly would not dispense a moisture-sensitive product in a cardboard box, he should appreciate this fact since he does do some repackaging. Note also that if a product is light-sensitive, it is important that this fact be stated on the label.

To exclude light, four main techniques are available: (a) wrap-around labels, (b) container coatings (some may incorporate ultraviolet absorbing materials), (c) various cartoning procedures, and (d) the use of so-called light-resistant containers. Since the latter are mentioned in the United States Pharmacopeia (2), we treat this area in some detail.

The light-transmission limits of glass and plastic containers are specified by the USP (2). These limits

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