

So the total reaction is



Most oxidations in pharmaceuticals occur in aqueous solution and are a function of the oxygen dissolved in the aqueous phase. In practice it is desired to minimize the decomposition, and it is a practice to remove oxygen from such systems by nitrogen flooding. Depending on the method used for the removal there can still be quite a bit of oxygen left in solution. Simple flooding is not effective, and to remove oxygen completely by boiling is rather difficult, and since oxygen has a low molecular weight, it can still be left present in sufficient (molar) excess to allow considerable oxidation. Hence, to free solutions of oxygen, nitrogen should be bubbled through them (the very best way of driving out dissolved oxygen). The use of antioxidants (bisulfite, ascorbic acid) is advocated where possible, in the case of oxygen-sensitive drug substances in solution.

In practice, complexing the heavy metals (e.g., by use of ethylene diamine tetraacetic acid) is often employed, since, as seen in the reactions sequences shown, metal ions are deleterious to drug stability in oxidative situations.

1.2. Quantitative Considerations in Oxidations in Two Phases

Most oxidation problems in the pharmaceutical sciences occur in systems (liquid or solid) that are in contact with a gas phase (usually air) that contains oxygen. As far as the methodology for following a decay, the monitoring of parent compound and decomposition products is what is usually carried out. If it is necessary to monitor oxygen concentrations, then Winkler's method (Winkler, 1888; Novaczyk et al., 1993) may be used, although it is cumbersome. Oxygen electrodes can also be used, but these are only good below 45°C. Finally, potentiometric titrations are possible. For work in the gas phase, Raman spectroscopy can be used. Most of what follows will concentrate on the disappearance of the parent drug.

Henry's law states, in the case of oxygen/water systems, that

$$P_{\text{O}_2} = K' X_{\text{O}_2} \approx K^* C \quad (4.13)$$

where C is the molar concentration and X the mole fraction of dissolved oxygen; K and K^* are Henry's law constants. For ordinary atmospheric conditions, $P_{\text{O}_2} = 0.22$ atm. At 25°C the value of K' for oxygen is 3.314×10^7 atm, i.e., the mole fraction of oxygen dissolved water would be $0.22/(3.3 \times 10^7) = 6.6 \times 10^{-9}$. The molar concentration corresponding to this is given by

$$X_{\text{O}_2} = \frac{C_{\text{O}_2}}{55.5 + C_{\text{O}_2}} \approx \frac{C_{\text{O}_2}}{55.5}$$

i.e., C_{O_2} is about 3.7×10^{-7} molar. Equation (4.13) is often expressed in inverse form, i.e.,

$$C = KP \quad (4.14)$$

where $K = 1/K^*$; both presentation forms will be used in the following.