1.1. Oxidation Mechanisms

Oxidation, as the word implies, is an interaction between drug substance, A, and oxygen, and the net reaction would be

$$A + O_2 \rightarrow \text{products} \tag{4.1}$$

However, oxidation reactions are usually the sum of a series of reactions (at times chain reactions), and these start with one particular reaction (the initiation reaction), which usually does not involve molecular oxygen. Frequently, oxidations are catalyzed by metal ions M^{++}; an example of this is the oxidation mechanisms reported for captopril (Timmins et al., 1982). Captopril contains a thiol group and will be symbolized as ASH below:

$$2ASH + 2M^{++} \rightarrow 2\{AS\cdot\} + 2H^+ + 2M^+ \tag{4.2}$$

$$2\{AS\cdot\} \rightarrow AS \cdot SA \tag{4.3}$$

$$2M^+ + O_2 \rightarrow 2M^{++} + O_2^{2-} \tag{4.4}$$

$$O_2^{2-} + 2H^+ \rightarrow H_2O + 0.5O_2 \tag{4.5}$$

where $\{\cdot\}$ denotes free radical. Hence, the overall reaction is

$$2ASH + 0.5O_2 \rightarrow AS \cdot AS + H_2O \tag{4.6}$$

It is noted that there is no net consumption of metal ion. (This latter has been chosen as being divalent in the above but could have other valences depending on metal in question). There is, however, a consumption of oxygen (otherwise there would be no oxidation). Upon exhaustion of oxygen, the oxidation would cease.

If oxygen is abundant, then of course all the drug can decompose, and in this case, as will seen below, the kinetics can be simply first order, since $[O_2]$ becomes (virtually) constant.

When captopril decomposes without presence of metals, it undergoes an autooxidation:

$$2ASH \leftrightarrow 2AS^- + 2H^+ \tag{4.7}$$

$$2As^- + 2O_2 \rightarrow 2\{AS\cdot\} + 2\{O_2\cdot\}^- \tag{4.8}$$

$$2As^- + 2\{O_2\cdot\} \rightarrow 2\{AS\cdot\} + 2O_2^{2-} \tag{4.9}$$

$$2\{AS\cdot\} \rightarrow ASSA \tag{4.10}$$

$$O_2^{2-} + 2H^+ \rightarrow H_2O + 0.5O_2 \tag{4.11}$$