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ORIGINAL ARTICLES

IL FARMACO, **49** (6), 431-435 (1994)

AUTOXIDATION OF DRUGS: PREDICTION OF DEGRADATION IMPURITIES FROM RESULTS OF REACTION WITH RADICAL CHAIN INITIATORS (*)

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Summary — In the study of the degradation of drug substances by molecular oxygen, their specific reaction mechanisms must be taken into account. The rate-determining step is usually the reaction of the substrate with a radical chain initiator, which is often an unknown impurity. The reactivity and selectivity of autoxidation can be controlled better by using a radical chain initiator, such as AIBN, than by changing the temperature or the oxygen pressure. In this paper the products profiles of four pharmaceutical substances in a simple oxidation test with AIBN are compared with the results of long term natural stability tests or with already established stabilities.

Stress testing is the basis of all studies of the stability of a new drug substance. The first aim of this kind of investigation is to discover the chemical and physical factors that can affect the stability of the molecule adversely, in order to design stable formulations. The second aim is to obtain samples of the drug contaminated with all possible and significant degradation impurities, in order to validate the analytical methods for the long term stability studies and to isolate the main impurities. While standard experimental conditions for the study of accelerated and long term stability are defined in all the regulatory guidelines, the protocol for the reactivity study must be fit to the particular chemistry of the molecule being examined. For investigation of the hydrolytic pathway of degradation, the general protocol is to study the effect of acids or bases at elevated temperatures on the stability of aqueous solutions of the drug substance, because it is well known that hydrolysis reactions are catalyzed by acids and bases. Oxidation is a more complex reaction, and the pharmaceutical literature describes stress testing with various oxidizing agents, such as hydrogen peroxide, heavy metal ions, acids, bases, high oxygen pressure, high temperature and, in some instances, strong oxidants such as potassium permanganate and chromic anhydride. Very often this literature emphasizes the poor predictiveness of this kind of stress testing. One reason for this poor predictiveness is that the operating mechanisms of the oxidation with the above reagents are completely different from the radical chain mechanism of autoxidation. Long term, room temperature degradation of an organic chemical is better simulated by using a radical chain initiator to accelerate the rate-controlling step of autoxidation. Use of this approach in the reactivity study has been described in the recent pharmaceutical literature[1-4]. In this paper the experimental conditions for use of some radical chain initiators and the predictivity of this kind of reactivity test for four examples will be discussed.

In the electronic structure of molecular oxygen[5], the highest occupied molecular orbitals are two degener π^* orbitals in which there must be two electrons. The ground state, according to the Hund rule, is the state in which each of these two orbitals is occupied by one electron, and the spins are parallel: this is the triplet ground state ($^3\Sigma g$) of the atmospheric molecular oxygen. Triplet dioxygen can be excited, both chemically and photochemically, to the first excited state with spin multiplicity 0, the singlet state $^1\Delta g$, 22 kcal higher than the ground state[5]. The triplet ground state is the state of dioxygen involved in autoxidation. The reactivity of triplet dioxygen toward organic molecules can be summarized as follows.

Electron-rich molecules such as pyrroles[6], α,β-unsaturated enamines[7], carbanions[5], 9,10-cyclopentane-4a,4b-dihydrophenanthrene[8], strained cycloalkenes[9] and, under more drastic conditions, tertiary amines, sulfoxides, alkenes and alkynes[10] can react with oxygen in an electron-transfer reaction:

$$R^- + (^3\Sigma g)\ O_2 \rightarrow R\cdot + O_2^{-\cdot} \qquad \text{(eq. 1)}$$

In addition, triplet oxygen reacts very fast with organic radicals:

$$R\cdot + (^3\Sigma g)\ O_2 \rightarrow ROO\cdot \qquad \text{(eq. 2)}$$

and this reaction is very important in propagation of radical chains.

However the vast majority of organic molecules are in the singlet state, and their reaction with triplet dioxygen:

$$RH + (^3\Sigma g)\ O_2 \rightarrow ROOH \qquad \text{(eq. 3)}$$

is spin forbidden. For this reason, a great many organic molecules, in spite of the large negative value of the Gibbs free energy of oxidation, are kinetically inert

(*) Presented at the V Convegno su recenti Sviluppi ed Applicazioni nell'Analisi Farmaceutica, Alghero, October 13-16, 1993.

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