RADIOLYTICAL MECHANISM OF CHLORAMPHENICOL AND ITS EYE OINTMENT DURING GAMMA STERILIZATION

L. HONG, and H. ALTORFER
Institute of Pharmaceutical Science, Federal Institute of Technology (ETH), 8057 Zürich, Switzerland

The influence of γ-irradiation on chloramphenicol (CAP) powder and its eye ointment (CAPEO) was investigated with High Performance Liquid Chromatograph. It was found that γ irradiation induced degradation of chloramphenicol both in eye ointment and in powder state, and the degree of degradation was proportional to the irradiation doses. At the irradiation dose of 25 kGy (the reference dose of γ sterilization [*1*]), CAP content decreases by 1.0 % in powder state, and by 3.3 % in eye ointment. Obviously, both the irradiation dose and the eye ointment base have played roles in the radiolytical degradation process.

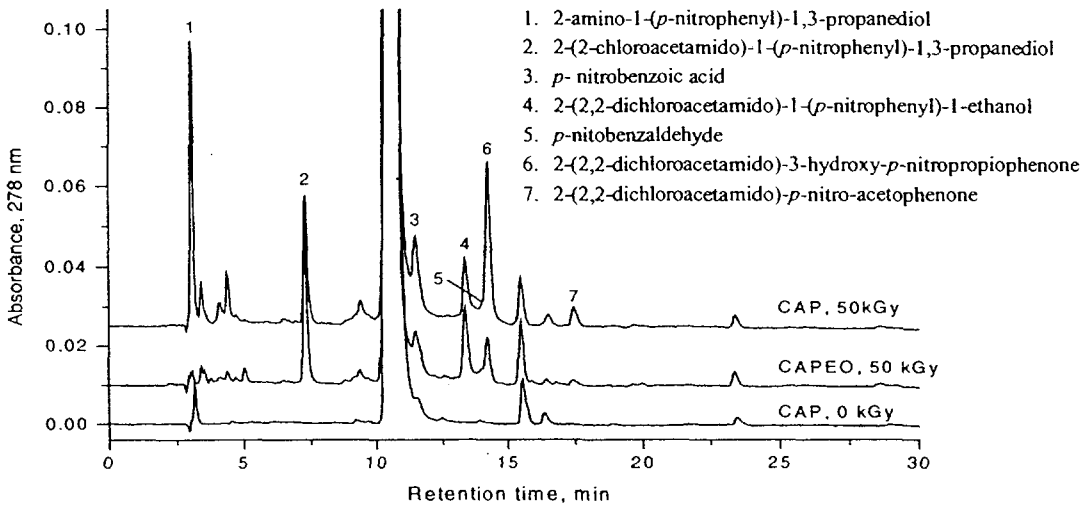

Figure 1. Typical HPLC chromatograms of radiolysis products of CAP powder and its eye ointment

By comparing the chromatograms of non-irradiated and irradiated chloramphenicol samples, seven compounds were found to be the main radiolysis products (Figure 1). The relative concentration of those compounds, as showed by the chromatograms, differs significantly between the irradiated CAP powder and CAP eye ointment samples, further suggesting that CAP in powder state and in eye ointment behaved differently under γ-irradiation processing.

In order to explore possible ways to eliminate this radiolytical degradation, such as protection techniques of scavenger, the degradation mechanism was first elucidated. HPLC-MS and reference compounds identifies the radiolytical products as shown in Figure 1. Compound 1 is a typical hydrolysis product of the acyl group of chloramphenicol [*2*], and compounds 6 is the oxidation product of the hydroxyl group (dehydrogenation). Formation of compounds 2 & 4 involves in substitution of hydrogen atoms (reduction), and compound 7 is a product of combined oxidation and reduction. Formation of compounds 3 & 5 involves all of the above reactions. It can be concluded that hydrolysis, oxidation and reduction are the main radiolytical degradation reactions of chloramphenicol products. The radiolytical mechanism was, therefore, elucidated in Figure 2.

The hydrolysis reaction is further illustrated by the behavior of compound 1, which only appears in CAP powder and not in CAPEO samples. Chloramphenicol in CAPEO was actually surrounded by the oily eye ointment base, which effectively separated the CAP ingredient from the atmospherical environment.

The same applies for the oxidation products as well. Compounds 6 and 7 were much smaller in CAPEO than in CAP powder samples, which could be inferred by the presence of oxygen in the case of CAP powder. The variation of peak 6, the direct product of oxidation, was more pronounced than that of peak 7, an indirect product (Figure 2).

Gamma irradiation certainly involves e_{solv}^- and will unavoidably promote the formation of hydrogen radical ($H^\bullet$, H_2, $HO_2^\bullet$), when the radiation energy is absorbed by the target substance. The radical reduction is therefore, unavoidable. This is demonstrated by the formation of compounds 2 & 4, the radical reduction products, which exist both in CAP powder and in CAPEO samples and with almost identical peak intensity, in regardless of the different micro environments.

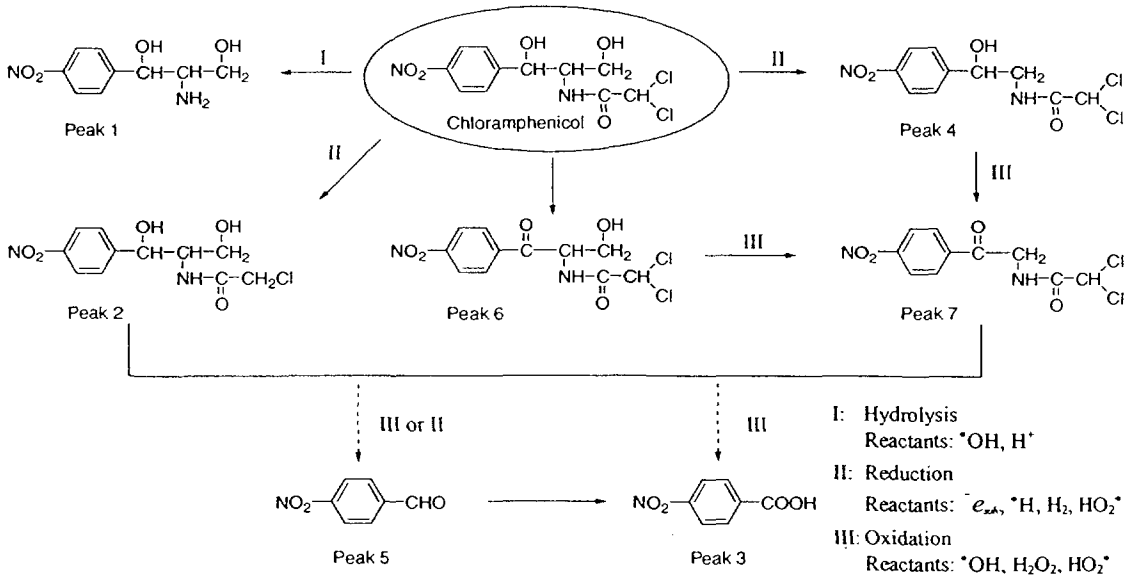

Figure 2. Radiolysis mechanism of chloramphenicol during γ radiation processing

The present experimental results clearly show that the matrix surrounding chloramphenicol during γ radiation played a critical role in the CAP degradation. Protection techniques to resist the radiolysis can therefore be established. Further experiments indeed show that indifferent gases (cleaning of the atmospherical environment) restrict the extent of radiolytical degradation of CAP powder, and radical scavengers, which capture the radicals, increase the stability of chloramphenicol during γ sterilization processing.

Reference

1. The European Agency for the Evaluation of Medicinal Products (EMEA). Decision Trees for the Selection of Sterilization Methods (CPMP/QWP/054/98); UK, **1999**; pp. 3.
2. Shih, I. K., Photodegradation Products of Chloramphenicol in Aqueous Solution. *Pharma. Sci.* **1971**, 60, 1889-1890.