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Gamma irradiation sterilisation of orciprenaline and fenoterol

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Abstract

The use of ionising radiation for sterilisation of drugs is now a well-established technology. In this paper, we have studied the stability of orciprenaline and fenoterol, two sympathomimetics, after gamma irradiation. High performance liquid chromatography (HPLC) chromatograms indicate that a dose of 25 kGy or lower slightly affects the amount of impurities. Gamma irradiation produces free radicals which appear relatively stable; these radicals could be detected even after a storage period of more than 12 months. The increase of free radicals versus dose was performed using polynomial regression analysis. Electron spin resonance (ESR) measurements could be used for the evaluation of the irradiation dose.

Keywords: Orciprenaline; Fenoterol; Gamma irradiation; Electron spin resonance; Free radicals; High pressure liquid chromatography; Radiolytic products

Radiation sterilisation technology and its applications in the manufacture of pharmaceuticals and cosmetics are being more actively investigated now than at any other time (Jacobs, 1995; Reid, 1995; Tilquin and Rollmann, 1996). Research carried in the early 1970s focused on the treatment of pharmaceuticals with high doses of radiation. This often resulted in unacceptable colour, odor and viscosity changes, as well as undesirable chemical changes. However, with the advances made in aseptic processing, we now have products and materials which are much cleaner, from a microbiological point of view, and thus are likely to require much lower radiation doses to achieve 10^{-6} SAL (sterility assurance levels). It may be the only way to sterilize many biological or biologically derived products, because of their sensitivity to heat.

Radiosterilisation, however, has the following two problems:

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- Gamma irradiation produces new radiolytic products; to prove the safety of radiosterilisation, it is important to determine the radiolytic products and elucidate the mechanism of radiolysis. High performance liquid chromatography (HPLC) is the analytical method of choice for the majority of drug stability protocols; it is a selective technique, allowing the separation and possible measurements of degradation products.
- The regulations governing radiosterilisation vary from one country to another. In the international market of the future, there will be a number of drugs that will be irradiated by gamma rays. Thus, it is desirable to establish a method to discriminate between irradiated and unirradiated drugs and to evaluate the dose of irradiation. Electron spin resonance (ESR) appears to be well suited to determine and quantify free radicals in complex media (Miyazaki et al., 1994).

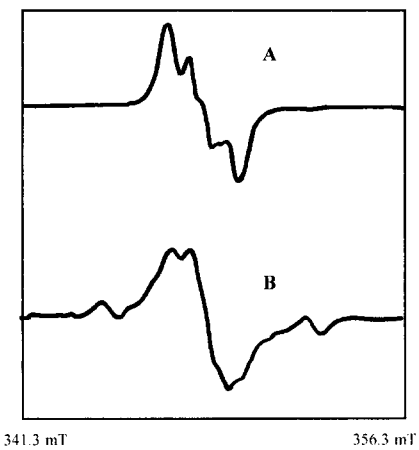
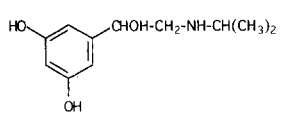


Fig. 1. ESR spectra

A: orciprenaline



B. fenoterol

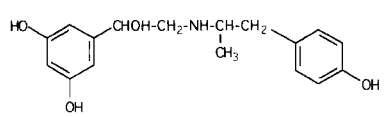


Fig. 1. ESR spectra.

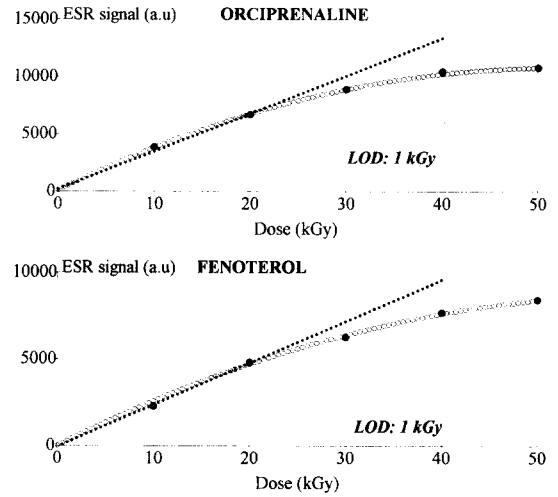


Fig. 2. Free radicals evolution with dose (room temperature).

The purpose of the present work was to investigate by ESR and HPLC the degradation of orciprenaline and fenoterol, two sympathomimetics, after gamma irradiation. Samples (30 mg) of orciprenaline sulfate and fenoterol bromide were irradiated with gamma rays emitted by an IBL 460; the dose rate was 1.6 kGy/h. The evolution of the ESR signal was followed by monitoring the maximum height (peak to peak) of the spectrum. To reduce noise in the ESR spectra, signals were accumulated.

Typical ESR powder spectra for orciprenaline and fenoterol after irradiation at 25 kGy are presented in Fig. 1.

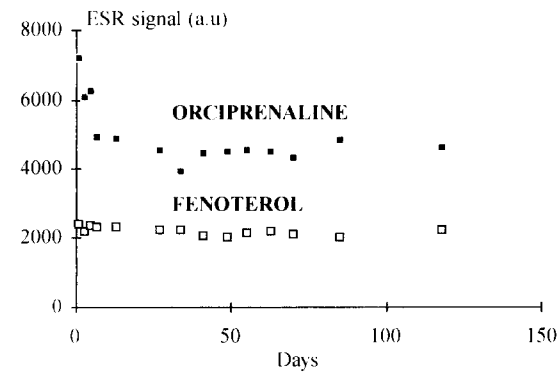


Fig. 3. Decay of radicals upon storage.

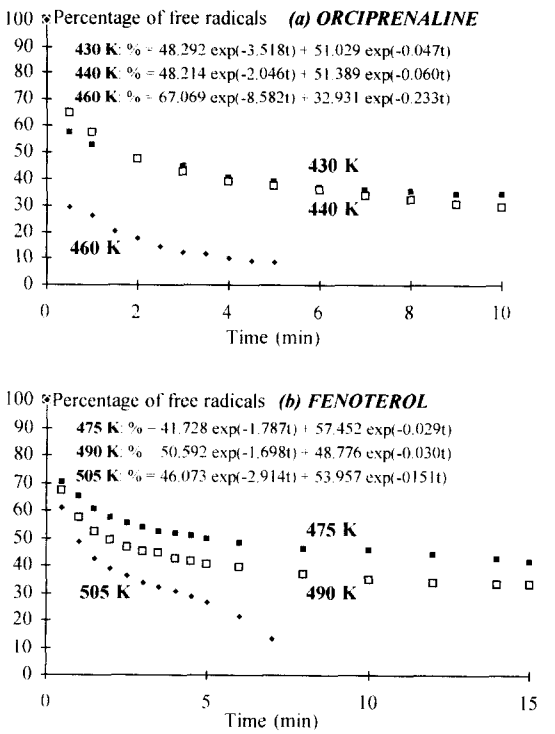


Fig. 4. Evolution of the percentage of free radicals with time for different temperatures.

Fig. 2 shows the free radicals evolution with dose at ambient temperature after gamma irradiation. Numerical simulation of the results was performed using linear regression (model a) and polynomial regression (model b):

- Model a: linear regression
  Orciprenaline: ESR signal (a.u) = $225 + 330D$
  Fenoterol: ESR signal (a.u) = $-10 + 240D$
- Model b: polynomial regression
  Orciprenaline: ESR signal (a.u) = $136.4 + 412.6D - 3.967D^2$
  Fenoterol: ESR signal (a.u) = $37.64 + 278.8D - 2.223D^2$

where D was the dose in kGy. The limit of detection (LDD) (Mehta, 1989) are 1 kGy. Since the irradiation dose currently used for radiosterilisation is 25 kGy, estimation of the dose by post-irradiation could be considered using the polynomial regression (model b).

Fig. 3 shows the decay of radicals upon storage in a sealed quartz tube after irradiation at 25 kGy. The free-radicals-decreasing kinetic of orciprenaline was simulated using a bi-exponential model as described in previous work (Basly et al., in press):

$$\text{ESR signal (a.u)} = 3249\exp(-0.1868t) + 4449\exp(-0.0002t)$$

where t was the storage time in days. Discrimination of irradiated drugs from unirradiated ones could be possible even after a storage period of more than 12 months.

The decay temperatures, defined as the temperatures corresponding to 5% (Gibella et al., 1993) and 50% radicals loss, respectively, are (345 K, 455 K) for orciprenaline and (380 K, 500 K) for fenoterol. The evolution of free radicals with time for different temperatures is presented in Fig. 4. The numerical simulation of the results was performed using a bi-exponential model:

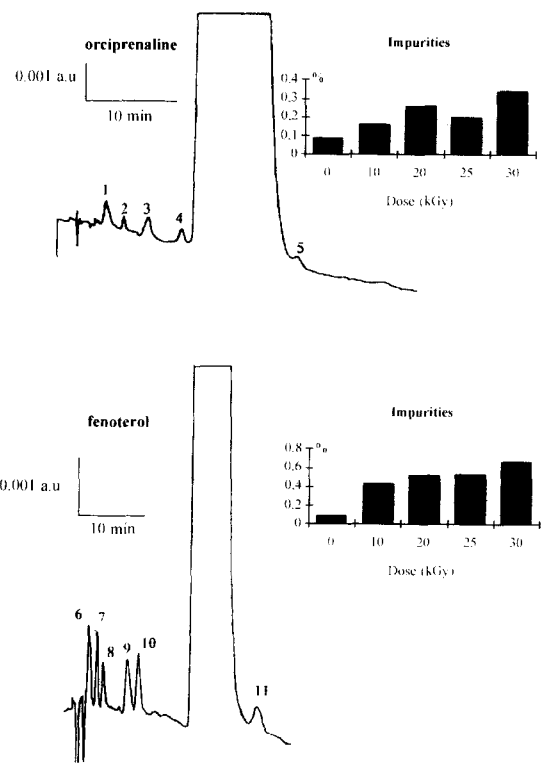


Fig. 5. Typical HPLC chromatograms after radiosterilisation.

$$\% \text{ free radicals evolution} = A \exp(-at) + B \exp(-bt)$$

where t is the time in minutes.

From these results, the decay could be divided into two phases, the first corresponding to a 'fast' pure exponential decay (coefficients A and a) and the second corresponding to a slower decay (B and b); this component could perhaps be attributed to a solid diffusion mechanism.

The impurity profiles were recorded using reversed phase HPLC. The chromatographic separation was based on the method described in the USP XXIII, following a slight modification in the methanol/buffer ratio. The chromatograms of irradiated samples are shown in Fig. 5. Other samples (irradiated or unirradiated) were examined and found to be similar in their impurity profiles. The amount of impurities and degradation products was determined at 280 nm for the two sympathomimetics. We assumed that the relative molar response factor (RRF) for an impurity was equal to one (i.e. the molar response factor of impurities at 280 nm were equal to the molar response factor of orciprenaline and fenoterol at 280 nm). The specific impurities after gamma irradiation were 1, 5 for orciprenaline and 8, 9, 10, 11 for fenoterol (Fig. 5). The increasing of the irradiation dose caused the amount (%) of impurities to increase (Fig. 5). Orciprenaline and fenoterol showed little degradation after gamma irradiation at 25 kGy.

In conclusion, from our initial results, doses of 25 kGy or lower slightly affect the amount of impurities; radiosterilisation of orciprenaline or fenoterol may be technically practicable. Some additional means of analysis will be necessary to validate the sterilisation by gamma radiation (e.g. structures of impurities).

Gamma irradiation produces free radicals which appear relatively stable; the shape of the decay curves versus time indicate that free radicals could be detected even after a storage period of more than 12 months. Estimation of the irradiation dose could be considered using ESR and a polynomial regression.

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