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Notes

Radiosterilization dosimetry by ESR spectroscopy: application to terbutaline

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Abstract

The use of ionizing radiation for sterilization of pharmaceuticals is now a well established technology. The purpose of the present work was to apply the electron spin resonance (ESR) spectroscopy to the irradiation dosimetry of terbutaline. Our preliminary work indicates that:

- evaluation of the irradiation dose could be possible by post-irradiation using a polynomial regression;
- the decay of radicals upon storage could be simulated by a bi-exponential regression; discrimination of irradiated drugs from unirradiated ones could be possible even after a storage greater than 3 years.

Keywords: Terbutaline hydrochloride; Electron spin resonance; Polynomial regression; Bi-exponential regression

Radiation sterilization 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 out in the early 1970s focused on the treatment of pharmaceuticals with high doses of radiation. This often resulted in unacceptable colour, odour 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 biologicals, or biologically derived products because of their sensitivity to heat.

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Radiosterilization, however, has the following two problems:

- gamma irradiation produces new radiolytic products; to prove the safety of radiosterilization, it is important to determine the radiolytic products and elucidate the mechanism of radiolysis;
- the regulations of radiosterilization are different among the countries. In the international markets 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 for determination of free radicals concentration in complex media. ESR measurements can also be used to detect and distinguish irradiated drugs from unirradiated ones (Miyazaki et al., 1994).

The purpose of the present work was to apply the ESR spectroscopy to the irradiation dosimetry of drugs. Samples (30 mg) of terbutaline hydrochloride, a beta-agonist, were irradiated with gamma rays emitted by a radioactive isotope (^{60}Co); 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.

Fig. 1. shows the free radicals evolution with dose at ambient temperature after gamma irradiation. Numerical simulation of the results were performed using linear regression (model a) and polynomial regression (model b): (a) ESR signal (a.u) $= -135.0 + 1122D$; (b) ESR signal (a.u) $= -616.8 + 1365D - 14.26D^2$ where D was the dose in kGy.

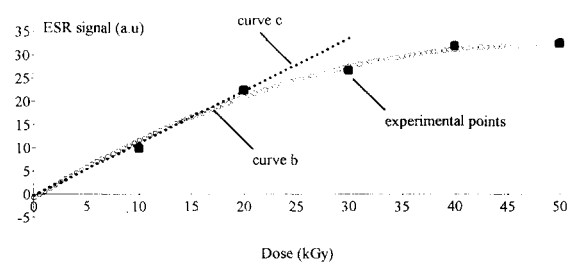

Fig. 1. ESR signal evolution with dose.

Table 1
Estimation of the errors[a] (%) on the ESR signal using linear regression (model a) and polynomial regression (model b)

Dose (kGy)	10	20	30	40	50
linear regression[b]	8.8	1.9	24.9	39.7	72.1
polynomial regression[c]	17.1	6.5	3.3	2.1	1.1

[a]error (%)

$$= \left| \frac{\text{ESR signal (calculated)} - \text{ESR signal (experimental)}}{\text{ESR signal (experimental)}} \right| \times 100.$$

[b]Linear regression (model a): ESR signal $= -135.0 + 1122D$.
[c]Polynomial regression (model b): ESR signal $= -616.8 + 1365D - 14.26D^2$ where D was the dose in kGy.

Estimation of the errors on the ESR signals using Eqs. (a) and (b) are given in Table 1. From this results, two points could be discussed:

- evaluation of the irradiation dose by comparison of the experimental ESR signal to the linear model (curve c) could only be possible for dose lower than 20 kGy; since the dose currently used for radiosterilization is 25 kGy, this method could not be used for terbutaline;
- estimation of the irradiation dose by post-irradiation could be considered using the polynomial regression (model b).

Fig. 2 shows the decay of radicals upon storage in a sealed quartz tube after irradiation at 25 kGy. The decay was simulated using a bi-exponential model (Plonka, 1991): ESR signal (%) $= 20.78 \exp(-0.1177t) + 79.22 \exp(-0.0001t)$ where t was the storage time in days.

As described in previous works (Basly et al., in press), the decay of radicals could be divided in two phases:

- the first corresponding to a fast 'pure' exponential model (curve d);

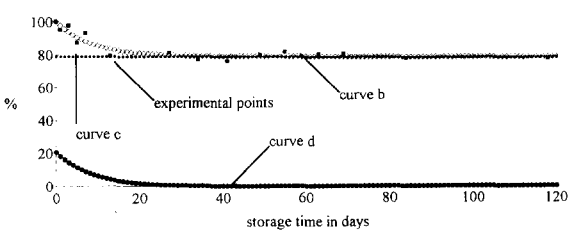

Fig. 2. Decay of radicals upon storage.

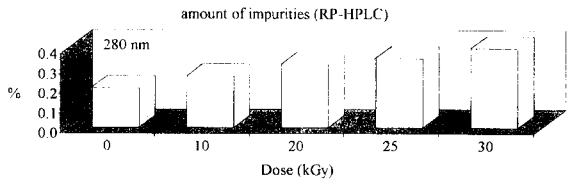

Fig. 3. Influence of radiation dose on the degradation of terbutaline.

– the second corresponding to a linear decay (curve *c*).

After 13 days of storage, the exponential component became negligible; during this time 20% of free radicals disappeared. Discrimination of irradiated drugs to non-irradiated ones could be possible even after a storage greater than 3 years.

The increase of the irradiation dose caused the amount of impurities to increase (Fig. 3).

In conclusion, this preliminary work shows the interest of the ESR spectroscopy in radiosterilization dosimetry.

Estimation of the irradiation dose could be possible if:

– the decay curve of the radicals upon time is measured;
– if the date of irradiation is known, the dose could be evaluated by post-irradiation using a polynomial regression.

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