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Notes

Gamma radiation induced effects on isoproterenol

A.L. Fauconnet[a], J.P. Basly[a,*], M. Bernard[b]

[a] *Laboratoire de Chimie Analytique et Bromatologie, Faculté de Pharmacie, Université de Limoges, 2 rue du docteur Marcland, 87025 Limoges Cedex, France*

[b] *Laboratoire de Biophysique, Faculté de Pharmacie, Université de Limoges, 2 rue du docteur Marcland, 87025 Limoges Cedex, France*

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Abstract

The use of ionizing radiation for sterilization of drugs is now a well established technology. Degradation of isoproterenol was investigated after gamma irradiation using HPLC and ESR. Chromatograms indicate that a dose of 25 kGy or lower slightly affected the amount of impurities. Gamma irradiation produces stable free radicals. Simulation of the increase of free radicals versus dose was performed using linear and polynomial regression. Irradiation dose ranging 10–25 kGy could be evaluated by post-irradiation using a linear regression.

Keywords: Dosimetry; ESR; HPLC; Isoproterenol; Gamma radiation

The sterilization of thermolabile medical devices, such as catheters or syringes, with ionizing radiation is successfully practised in many countries. Futhermore, it is possible to sterilize pharmaceutically active subtances with ionizing radiation (Jacobs, 1995; Reid, 1995; Tilquin and Rollmann, 1996; Boess and Bögl, 1996). The advantages of sterilization by irradiation include high penetrating power, low chemical reactivity, low measurable residues, small temperature rise and the fact that there are fewer variables to control. Thus the sterilization can be carried out on finally packaged products.

High performance liquid chromatography (HPLC) is the analytical method of choice for the majority of drug stability protocols. It is a very selective technique allowing the separation and possible measurements of degradation products.

Electron spin resonance (ESR) appears to be very suitable for the determination of free radicals concentration in complex media. ESR measurements can also be used to detect and distinguish irradiated drugs from unirradiated ones

* Corresponding author. Tel.: + 33 5 55435898; fax: + 33 5 55435801.

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(Miyazaki et al., 1994).

Following previous studies (Basly et al., 1996), the purpose of the present work was to investigate the degradation of isoproterenol, a β-sympathomimetic, by ESR and HPLC.

Samples (30 mg) of isoproterenol hydrochloride were irradiated with γ rays emitted by a radioactive isotope (^{60}Co); the dose rate was 1.7 kGy/h. One unirradiated sample was kept as reference.

The impurity profiles were recorded using reversed phase HPLC. The chromatograms of irradiated samples are shown in Fig. 1. Other samples (irradiated or unirradiated) were examined and found to be similar in their impurity profiles. The amount of impurities and degradation products

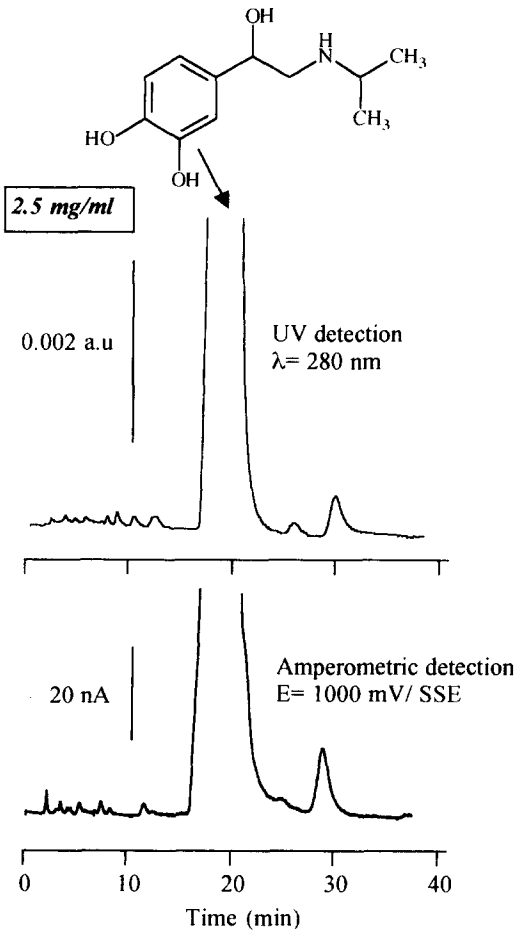

Fig. 1. Typical HPLC chromatograms after radiosterilization (25 kGy).

Table 1
Influence of radiation dose on the degradation of isoproterenol (mean of three samples)

Dose (kGy)	Purity (%)	S.D. (%)	Storage (days)
—	99.98	0.02	—
5	99.94	0.05	3
10	99.84	0.02	214
10	99.80	0.02	—
15	99.90	0.03	5
15	99.92	0.02	5
20	99.90	0.04	4
25	99.89	0.04	214
25	99.79	0.02	4
30	99.90	0.05	2
35	99.91	0.05	—
40	99.90	0.06	—
45	99.87	0.06	—
50	99.80	0.03	—
200	99.40	0.08	797

were determined at 280 nm. We assumed that the relative molar response 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 isoproterenol at 280 nm). Isoproterenol showedlittle degradation after gamma irradiation (Table 1).

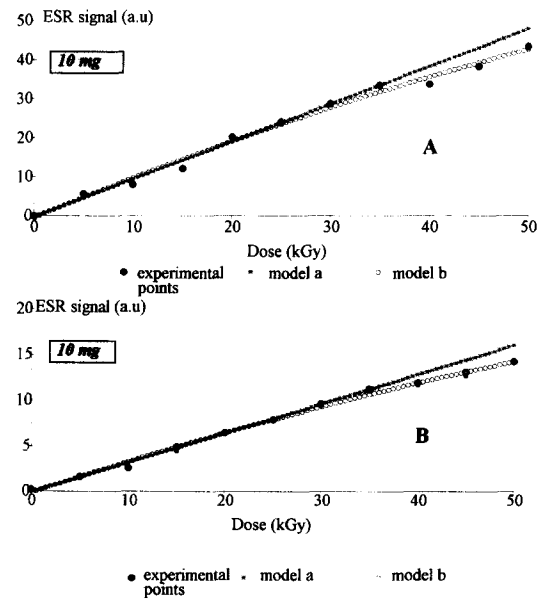

Fig. 2. Free radicals evolution with dose (room temperature).

Table 2
Control of the radiosterilization dose by post-irradiation

Sample	1	2	3	4	5	6	7	8
Irradiation dose (kGy)	10	10	15	15	20	20	25	25
Post-irradiation (kGy) (peak to peak height)	8.5	8.5	13.0	14.0	21.5	20.5	28.0	26.0
Post-irradiation (kGy) (double integration)	8.5	11.5	13.0	14.5	21.0	20.0	27.5	24.0

ESR can be used as identification test if:
- the radicals are quit stable with regard to the maximum time of storage;
- the relative signals must be distinguishable from the ones of the reference samples;
- the signals must be strictly constant if we also require an estimation of the irradiation dose.

The evolution of the ESR signal for doses ranging 0–50 kGy was followed by monitoring the maximum height (peak to peak) or by double integration of the spectrum.

Numerical simulation of the results were performed using linear regression (model a) and polynomial regression (model b). (a), ESR signal (a.u) $= \alpha + \beta D$ and (b), ESR signal (a.u) $= \gamma + \delta D + \varepsilon D^2$ where D was the dose in kGy and εD^2 was introduced as a corrective term.

Fig. 2 shows plots of the evolution of ESR signal versus dose. Each point was the mean of three samples and the coefficients of variation for each dose were lower than 5% except 40 kGy (7.6%). Limit of quantification (Mehta, 1989) was inferior to 2 kGy.

Tests were carried out to investigate whether storage had an effect on the free radicals concentration. Storage at ambient temperature in a sealed quartz tube over several weeks (132 days) showed no variation of the ESR signal (Fig. 3)

Assuming that estimation of the dose by post-irradiation could be considered using linear regression for doses lower than 30–40 kGy, post-irradiation (+ 5 kGy, + 10 kGy and + 15 kGy) was applied to eight samples. Results are given in Table 2.

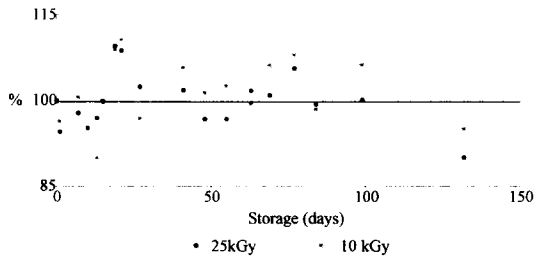

Fig. 3. Decay of radicals upon storage.

In conclusion, from our firstly results, doses of 25 kGy or lower affect slightly the amount of impurities; radiosterilization of isoproterenol may be technically practicable. Some additionnal means of analysis will be necessary to validate the sterilization by gamma radiation.

Gamma irradiation produces stable free radicals. An increase of free radicals versus dose could be simulated by linear or polynomial regression. Irradiation doses ranging from 10 to 25 kGy could be evaluated by post-irradiation using linear regression.

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