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Electron spin resonance—thermoluminescence studies on irradiated drugs and excipients

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Abstract

The methods (ESR, TL, GPC) developed to prove whether or not a foodstuff has been irradiated can be used to get the same proof in case of an irradiation treatment of drugs, excipients and cosmetic products. © 2002 Elsevier Science Ltd. All rights reserved.

Keywords: Drug; Excipient; ESR; Thermoluminescence; Gamma irradiation

1. Introduction

Gamma rays and electron beams have been used for a long time in order to sterilise medical devices. This treatment will be applied more and more for sterilisation of drugs. As for foodstuffs (Raffi, 1998), it could be interesting to be able to prove whether or not a drug has been irradiated.

For drugs irradiated in solid and a relatively dry state, the induced and trapped radicals and ions can be detected by electron spin resonance (ESR) or by thermoluminescence (TL). Another technique, gas phase chromatography, which is based on the radio formation of hydrocarbons deriving from lipids was also used to detect irradiated foodstuffs: this technique may also be applied in the case of creams and cosmetic products.

2. Electron spin resonance (ESR)

A lot of drugs and excipients can be irradiated in solid state; generally, they show no ESR signal in the unirradiated sample which is consequently very easy to be detected. However, we note that radicals detected by

ESR can also be induced by other treatments such as UV radiation or by mechanistic action such as grinding: the main radicals induced into starches by gamma (Raffi and Agnel, 1983) or UV radiation (Bertolini et al., 2001), or by grinding are identical; other excipients such as lactose (Fig. 1A), carboxymethylcellulose (Fig. 1B), cellulose, mannitol,... may also present ESR signals due to grinding but these signals are always very weak with regard to the radio-induced ones. Thus, we can consider that for a synthetic drug, there is no signal present in the unirradiated sample; on the other hand, the drugs being dry, the lifetime of the signals induced by radiation is very long: several months or years (see Fig. 2 for the example of an antibiotic) (Gibella et al., 2000). Consequently, ESR detection of irradiated drugs is very easy.

However, in the case of natural products used in some drugs, the unirradiated sample may also present a single line very often found in vegetal products, probably due to a quinone radical (Raffi and Agnel, 1989); but this single line is easy to distinguish from the complex signal induced in the irradiated drugs.

3. Thermoluminescence (TL)

Here too, this method must be applied to drugs irradiated in powder and dry state, allowing the

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Fig. 1. ESR spectra of radicals induced by grinding in lactose (A) and carboxymethylcellulose (B)

Fig. 2. ESR spectra of radicals induced in anhydrous ampicillin acid just after a 50 kGy irradiation (left) and six months later (right).

detection of radio-induced ions trapped in the solid matrix. Contrary to the protocol used for the detection of irradiated products where the TL signal is due to silicate impurities (CEN, 1996/97-a), there is no problem of extraction; the signal is easy to be recorded (Stocker et al, 1999).

But the study may be more complex. First of all, the unirradiated sample presents a TL spectra as the unirradiated one, for instance, two peaks in the case of anhydrous ampicillin acid (Fig. 3); in this favourable case, the two peaks vary on different ways with regard to the irradiation dose and thus lead to a proof of irradiation. But in other complex antibiotics, the peaks may have entirely different variations (Stocker et al., 1999). Consequently, each drug is a different case and

requires a specific study. There will not be a general detection protocol as in case of foodstuffs.

4. Gas phase chromatography (GPC)

In the case of drugs containing lipids, we could try to apply the protocol devoted to foodstuffs containing lipids (CEN, 1996/97-b) as the percentage of radio-induced hydrocarbons is directly linked to the chemical composition of lipids; this is due to the fact that, when fatty acids are exposed to high energy radiation, they undergo preferential cleavages, unlike other treatments, in the ester carbonyl region; the two main hydrocarbons, derived from each fatty acid of structure $C(n:m)$ are those of structure $C(n-1:m)$, with one carbon less than the parent fatty acid and of structure $C(n-2:m+1)$, with two carbons less and one extra double bond.

In fact, the problem will be that main cosmetic products, or creams used as vectors in pharmacopoeia to transfer a drug through the skin, have complex compositions which probably does not allow us to reach, in each case, a proof of the irradiation treatment.

5. Experimental section

5.1. Grinding experiments

Grinding was performed in a vibro-activator (one-ball vibration mill of type *Dangoumau*). Dangoumau grinder has been used to study phase transformations of minerals, and recently to increase bioavailability of drugs by co-grinding. (Baron et al., 1998).

5.2. Irradiations

They were performed in the "CIGAL" cell of Cadarache (80 000 Ci of cobalt 60) supplying a dose rate of 8.5 kGy h^{-1} .

Fig. 3. TL recording (left) of unirradiated anhydrous ampicillin acid and variation of peak intensities (right) with irradiation dose (kGy).

5.2.1. ESR and TL measurements

The spectra were recorded, respectively, with a Bruker EMS104 spectrometer and a Harshaw 4000 A apparatus.

6. Conclusions

Thus, we can ascertain that, for drugs and cosmetic products, we can write in the future some protocols of detection for an irradiation treatment if:

the product is irradiated in solid and dry state, by ESR in every case, and by TL at least in some cases; the product is rich in lipids, by GPC, at least in some cases.

But, before writing these protocols, there will be a lot of fundamental researches to carry out.

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