# Study of dosimetric properties of acetylsalicylic acid in pharmaceutical preparations by EPR spectroscopy

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**Abstract.** Electron paramagnetic resonance (EPR) was used to investigate the dosimetric properties of two pharmaceutical preparations containing acetylsalicylic acid, Aspirin® and Cafiaspirin®. The EPR spectra of the irradiated samples were found to have an asymmetric absorption characterized by a major resonance at $g$ = 2.0033. Dose response was investigated between dose ranges of 2 to 40 kGy for $^{60}$Co-gamma rays. Fading characteristics and dependence on temperature irradiation were also studied. We suggest that commercial Aspirin® and Cafiaspirin® tablets can be used as dosimeters for industrial processes.

***KEYWORDS: dosimetric properties, pharmaceutical preparations, acetylsalicylic acid, EPR.***

## 1. Introduction

Electron paramagnetic resonance (EPR) and thermoluminiscence (TL) techniques have a great potential for radiation dosimetry characterized by non-destructive evaluation of radiation quantities delivered to different materials. The advantage that EPR measurements have is that they can be done without heating the material.

EPR signals can be obtained when unpaired electrons occur at defects in solids but in many cases this condition is brought about by irradiation of the solid with energetic radiation or particles giving opportunity for the formation of free radicals due to a rupture of chemical bonds. The area under the doubled-integrated EPR signal is related to the number of paramagnetic centers, which in turn is related to the amount of radiation imparted to the substance, Engin [1]. Some of the main features of a good dosimeter are to be sensitive to radiation in a wide range, stable over a long time period, reproducible, and energy independent.

Interest in EPR dosimetry extends from high doses (kGy) as used in food irradiation, sterilization of medical supplies, industrial waste treatment and radiation polymerization, to lower doses (< 1Gy) , as in emergency dosimetry and extreme situations or accidents of occupational exposure and area monitoring. In order to improve the ease of sample handling, the reproducibility of signal detection, and to test the stability of samples for futures measurements and possible archiving some methods of incorporating different substances have been adopted, Tchen [2].

The aim of this project is to investigate the potential use of gamma irradiated acetylsalicylic acid in solid pharmaceutical tablet preparations as normal dosimetric systems.

We investigated the EPR spectral features for the quantification of the species produced by radiation and to correlate them with dose response curves.

Other features studied are: Dose effect (2 to 40 kGy), irradiation temperature dependence (293 K and 77 K) and fading.

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Irradiated pharmaceutical preparations may form radical species arising from active and non medicinal ingredients present in the preparation. In the case of Aspirin® and Cafiaspirin®, starch is added as non medicinal ingredient.
According to Cozar [3], three types of radicals occur by γ–irradiation of pure acetylsalicylic acid, two of which are the result of hydrogen abstraction while the third is produced by hydrogen addition to one of the carbon atoms of the aromatic ring. There is a relative yielding of the free radicals as a function of absorbed dose. The first radical gives rise to a single central line centered at $g$ = 2.008 and the second free radical is responsible for the triplet superimposed on the central line. These radicals are in the form ROO• and R-$CH_2$•. The triplet is centered at $g$ = 2.0028 and a simulated spectrum is due to a mixture of the three radicals present simultaneously.
Bertolini [4] has established that EPR experiments have made a major contribution to our understanding of the mechanism of starch degradation after gamma irradiation and it has been reported that gamma irradiation of starch induces free radicals at the $C_1$ position on the glucose molecule.
On the other hand, Muñoz [5] has studied by EPR the irradiated ground corn and he proposed the use of this substance as a dosimeter. He concluded that exist three types of radicals with different half-lives, but the irradiation process induces the formation of free radicals at $g$ = 2.004±0.002. Raffi [6] has found that many drugs and excipients such as mannitol, cellulose, and starch can be irradiated in solid and dry state and generally they show no EPR signal in the unirradiated sample which is consequently very easy to detect.

## 2. Experimental

*Samples*
The acetylsalicylic acid samples were acquired as commercial products in a drugstore in Mexico City (Aspirin® and Cafiaspirin® from Bayer® Laboratories). Tablets of Aspirin® were used with 600 mg weight (500 mg of acetylsalicylic acid and 100 mg of starch as excipient) and tablets of Cafiaspirin® with 650 mg weight (500 mg of acetylsalicylic acid, 30 mg of caffeine and 120 mg of excipient). Samples were used in their original primary pharmaceutical pack without any treatment.

*Irradiation*
Irradiation was performed with a 60-cobalt Gammabeam 651 PT irradiation source with nominal activity of $2.96x10^{12}$ kBq in February 2007. The absorbed doses were between 2 and 35 kGy at a fix position with a dose rate of 159 Gy/min. Some samples were irradiated at room temperature (293 K) and others at liquid nitrogen temperature (77 K) inside a Dewar flask. Dose rate was determined with ferrous ammonium sulfate-cupric sulfate dosimeter.

*EPR measurements*
The EPR analysis was carried out at Instituto de Química-UNAM with 30±0.1 mg of the sample, in a quartz tube at room temperature with a Jeol JES-TE300 spectrometer operating at X-Band fashions at 100 KHz modulation frequency and a cylindrical cavity in the mode $TE_{011}$. The external calibration of the magnetic field was made with a precision gaussmeter, Jeol ES-FC5. The spectrometer settings for all spectra were as follows: center field, 336.0 mT; microwave power 8 mW, microwave frequency 9.43 GHz; sweep width, ± 7.5 mT, modulation width, 0.1 mT; time constant, 0.1 s; amplitude, 200; sweep time 120 s; accumulation, 1 scans. In order to know the concentrations of radicals or spins for dosimetric purposes, the measurement of concentration was made by double integration of the signal using TEMPOL (4-hydroxy-2,2,6,6-tetramethyl-piperidinyloxy, free radical) as the standard. These values were used for constructing the dose-response curve.
Spectral acquisition and manipulations were performed using the program ESPRIT-382, v1.916. The EPR spectra were recorded as a first derivation and the main parameter such as $g$-factor values were calculated according to Weil [7].
All samples, irradiated and non-irradiated, were stored for 24 hours at room temperature prior to EPR analysis. The results are given as replicate of three different samples.

EPR spectra for components of the pharmaceutical preparations under study were also investigated for comparison purposes, acetylsalicylic acid as a reagent (99%, from Sigma Co.), corn starch (as excipient) and caffeine. Fig. 1 shows the EPR spectra for these components.

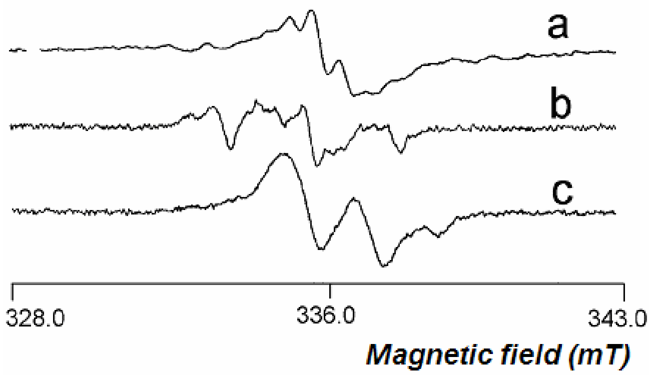


Fig.1. EPR spectra for the γ–irradiated components of the pharmaceutical preparations:
a) caffeine (28 kGy), b) acetylsalicylic acid (14.3 kGy) and c) corn starch (15 kGy)

## 3. Results and discussion

Both, Aspirin® and Cafiaspirin® exhibited an EPR spectrum due to the free radicals produced by gamma irradiation. The non-irradiated samples do not exhibit these signals.

The color of the tablets changes from white to light gray while pH of dissolution changes from 2.7 for a non-irradiated tablet in 100 mL of distilled water to 3.0-3.5 for an irradiated tablet according to the increased dose.

Aspirin® and Cafiaspirin® EPR spectra features consist in many resonance lines and they show that, the radicals contributing to signal have the same origin. The spectra show an asymmetric absorption at $g$ = 2.0033 (central line) and for both preparations, their intensity increased with the irradiation dose.

Table 1 shows the spin number in terms of concentration and arbitrary units as a function of the absorbed dose for Aspirin® irradiated at 293 K.

Table 1. Spin number as a function of the absorbed dose for Aspirin® tablets γ-irradiated at 293 K

| Dose (kGy) | Spin number ($10^4$) (mol/L) | Arbitrary units (a.u.) |
|---|---|---|
| 0 | 0 | 0 |
| 2.4 | 0.26 | 1.0 |
| 4.8 | 0.59 | 2.3 |
| 9.5 | 1.12 | 4.3 |
| 14.3 | 1.96 | 7.6 |
| 23.8 | 3.48 | 13.4 |
| 38.2 | 3.50 | 13.5 |

Fig. 2 shows a typical EPR signal for Aspirin® irradiated at 293 K and at different absorbed doses. The spectrum corresponds to all free radicals, as a sum, simultaneously present from the active principle and the excipient. As it can be observed, the shape of the spectrum is independent of the applied doses in the range studied (2-40 kGy).

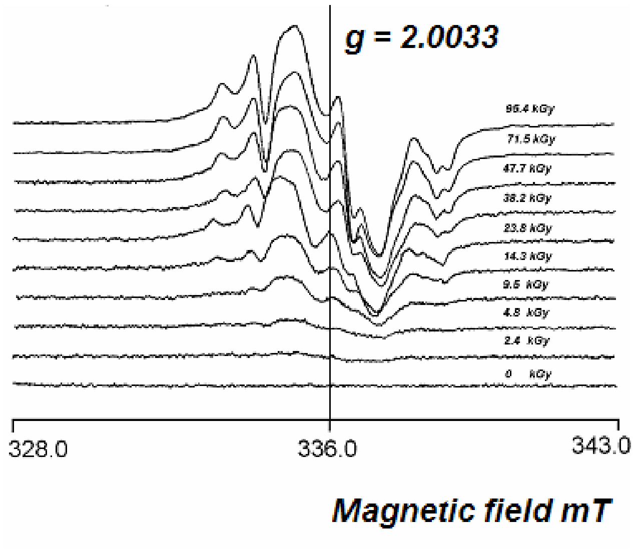


Fig.2. EPR spectra for Aspirin ® tablets γ-irradiated at 293 K

*Dose-rate dependence*

Dose-rate dependence was also investigated using 159 Gy/min and 239 Gy/min. For all the samples, no changes were observed either in the shape of the spectrum or in the EPR line amplitude ($g$ = 2.0033). We propose that EPR sensitivity of the samples is independent of the dose-rate.

*Response to dose irradiation*

The response for Aspirin® and Cafiaspirin® tablets to $^{60}$Co gamma radiation is presented in Fig. 3 as EPR signal intensity in arbitrary units versus absorbed dose in the range 2-40 kGy. There is a linear response found in the range 2 to 10 kGy.

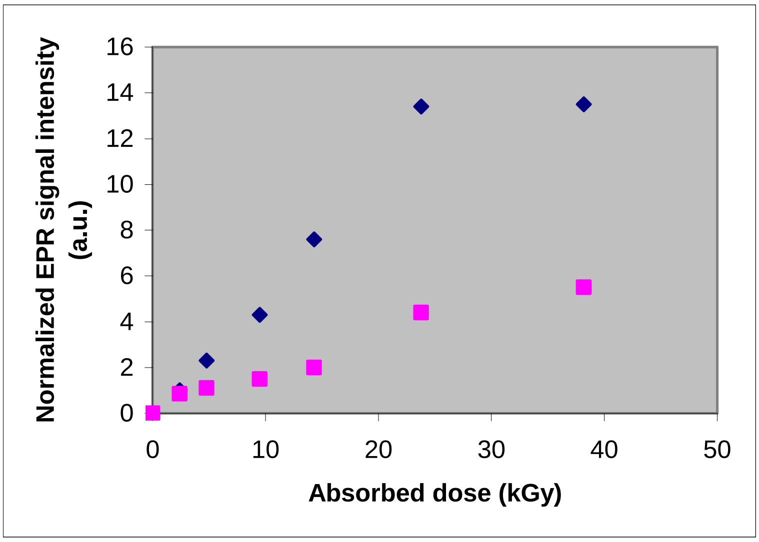


Fig 3. Normalized EPR signal intensity vs. absorbed dose for ♦Aspirin® and ■Cafiaspirin® tablets γ-irradiated at 293 K.

*Stability of the signals*

Time stability of the irradiation-induced radicals in the preparations is an important factor to consider for dosimetric purposes. A study of the stability of the EPR signals in long term was performed to observe the decay or fading of the signal. The samples irradiated at 38 kGy were used and the measurements were performed during 20 days of storage, keeping the samples at room temperature, in a dry place, protected from light. Their spectra were recorded in regular intervals. The signal intensity was found to decrease with the storage time but it still could be detected after 20 days. Corrections must be made for calculating the initial dose received by the sample. For Aspirin® tablets, the decline in signal intensity is about 56% in 7 days and about 70% in 15 days.

*Irradiation temperature dependence*

When Aspirin® is irradiated at low temperature (77 K), the concentration of free radicals increases by comparison with Aspirin® irradiated at 293 K. This is a typical behavior for paramagnetic samples, because of the signal increases when the temperature is decreased.

## 4. Conclusions

We study the behavior under irradiation of two solid pharmaceutical preparations containing acetylsalicylic acid (Aspirin® and Cafiaspirin®). We have used the EPR spectroscopy to follow the variation of signals with the increased gamma-absorbed dose at two different temperatures. The radicals species originated from the acetylsalicylic acid dominate the EPR spectrum of both preparations but the other non medical components (starch) contributed to this signal.

Dose response curve shows a linear behavior in the range 2-10 kGy. These commercial products have good dosimetric features, characterized by their EPR spectra and storage capacity. These products can be proposed as potential candidate materials to monitor the radiation on industrial processes at room temperature (293 K).

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