

Investigation of radiosterilization and dosimetric features of sulfacetamide sodium

Şeyda Çolak, Mustafa Korkmaz*

Physics Engineering Department, Hacettepe University, 06800 Beytepe, Ankara, Turkey

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Abstract

In the present work, the spectroscopic and kinetic features of the radical species induced in gamma-irradiated sulfacetamide-sodium (SS) was studied at room and at different temperatures in the dose range of 5–50 kGy by electron spin resonance (ESR) technique with the aim of investigating the possibility of radiosterilization and dosimetric features of SS. A model consisting of four radical species of different spectroscopic features denoted as I–IV was found to describe best whole experimental data derived throughout the present work. These species were quite stable at room temperature but relatively unstable above room temperature. Heights of the characteristic resonance peaks measured with respect to the base line were considered to monitor microwave, temperature, time dependent and kinetic features of the radical species contributing to ESR spectrum. Collected experimental data were used to characterize the radical species responsible from ESR spectra through simulation calculations. Possible changes in the IR bands of gamma irradiated SS was also investigated by FT-IR technique, but no definite difference was observed between unirradiated and irradiated IR spectra of SS. As in other sulfonamides, radiation yield of solid SS was found to be very low ($G \leq 0.1$), therefore basing on this result it was concluded that SS and SS containing drugs could, safely, be sterilized by radiation and that SS did not exhibit good dosimetric features.

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1. Introduction

Gamma radiation; which is a useful, efficient and economic tool for the sterilization of many samples in their final containers is more actively used nowadays [1–6]. High penetrating power, low chemical reactivity, low measurable residues, small temperature rise and fewer variables to control are the advantages of sterilization by irradiation [7,8]. With the publication of EN 552 and ISO 11137, there is at least a recognized standard for implementing radiation technology [9,10]. Since ionizing radiation causes degradation such as creating reactive molecular fragments in the samples which may result in a toxicological hazard, the adoption of

this method requires detailed investigations to ensure that no untoward changes take place [10–13].

Electron spin resonance (ESR) spectroscopy is one of the leading methods for identification of irradiated foodstuffs and, recently, has proven to be an accurate and reliable technique for irradiation dosimetry of pharmaceuticals even for small radiation doses [14]. It yields both, qualitative information (i.e. whether or not a sample has been irradiated) and quantitative results (i.e. the dose it received) so by this method it is possible to detect and to distinguish irradiated drugs from unirradiated ones [15,16]. Moreover ESR has other preferential properties such as high sensitivity, precision, ease and non-destructive readout [17]. Previous results [11,18,19] have already shown the suitability of ESR for the detection of some specific irradiated antibiotics. In this paper, we examine the potentialities of ESR spectrometry as analytical tool in the

* Corresponding author. Tel.: +90 312 297 72 13;
fax: +90 312 299 20 37.

E-mail address: seyda@hacettepe.edu.tr (M. Korkmaz).

investigation of radiosterilization and dosimetric features of SS.

2. Materials and methods

Sulfacetamide-sodium (SS) is one of the commonly used sulfonamide as antibacterial agent to treat infections caused by bacteria topically for eye and skin infections, orally for urinary track. SS contains not less than 99% and not more than the equivalent of 101% of the sodium derivative of *N*-[4-aminophenyl sulphonyl] acetamide calculated with reference to anhydrous substance [20]. SS is a white or yellowish white, crystalline powder which slowly darkens on exposure to light and/or on exposure to moist air [21].

SS is provided from Faculty of Pharmacy of Hacettepe University (Ankara) and was stored at room temperature in a well closed container protected from light. No further purification was performed and it was used as it was received. Irradiations were performed at room temperature using a ^{60}Co gamma cell supplying a dose rate of 2.5 kGy/h as an ionizing radiation source at the Sarayköy Establishment of Turkish Atomic Energy Agency in Ankara. The dose rate at the sample sites was measured by a red perplex dosimeter. Investigations were performed on samples irradiated at four different doses (5, 10, 25, 50 kGy).

ESR measurements were carried out using Varian 9'-E line-X band ESR spectrometer operating at 9.5 GHz and equipped with a TE₁₀₄ rectangular double cavity containing a standart sample (DPPH) in the rear resonator which remained untouched throughout the experiment. Signal intensities were calculated from first derivative spectra and compared with that obtained for a standart sample (DPPH) under the same spectrometer operating conditions. Sample temperature inside the microwave cavity was monitored with a digital temperature control system (Bruker ER 4111-VT). The latter provided the opportunity of measuring the temperature with an accuracy of ± 0.5 K at the site of the sample. A cooling, heating and subsequent cooling cycle was adopted to monitor the evolution of the ESR line shape with temperature using samples irradiated at room temperature. The latter was first decreased to 140 K starting from room temperature, then increased to 400 K with an increment of 20 K and finally was decreased again to room temperature. Variations in the line shape and in the signal intensities with microwave power were also studied in the range 1–80 mW for samples irradiated at room temperature.

Kinetic studies of the contributing free radicals were performed at different temperatures. The samples irradiated at room temperature were heated to predetermined temperatures (358, 393 and 413 K) kept at these temperatures for predetermined times (3, 5, 8, 10, 13, 16, 20, 26, 30, 35, 41, 45, 55, 60, 80, 90, 120, 160, 220 min), then they were cooled to room temperature and their ESR spectra were recorded. The results were the average of five replicates for each radiation dose. A simulation calculation based on a model of four

radical species anticipating from the results of microwave saturation, variable temperature, decay at normal and stability conditions, dose–response and annealing studies, was performed to determine the spectroscopic features of the contributing free radicals.

3. Experimental results and discussion

3.1. General features of the ESR spectra

No signal was detected for unirradiated SS. A complex ESR spectrum consisting of seven characteristic resonance peaks (Fig. 1a–c) was observed to be specific to the gamma radiation treatment of SS. The resonance peak appearing in the middle of the spectrum was found to have $g = (2.0045 \pm 0.0004)$ and peak to peak width $\Delta H_{pp} = (5.5 \pm 0.2)$ G. Increase in the absorbed dose did not create any pattern change in the spectra of the irradiated samples. Thus, it was concluded that irradiation dose was not an important parameter in the determination of the shape of ESR spectrum of SS in the adopted radiation dose range.

3.2. Microwave saturation characteristics of the assigned peaks

Variations of the heights of the assigned resonance peaks (Fig. 1a) with applied microwave power were studied first in the range of 1–80 mW. All height measurements were performed with respect to spectra baselines and were normalized to the receiver gain, the mass of the samples and the intensity of the standard. The results of these studies indicated that

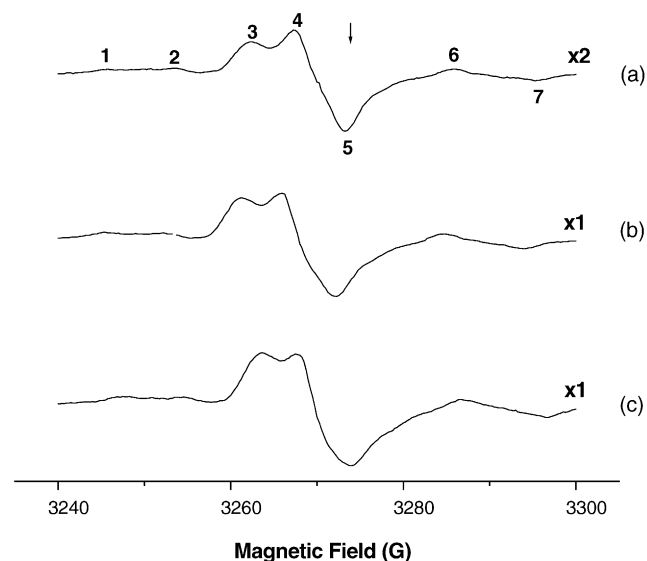


Fig. 1. Room temperature ESR spectra recorded at three different microwave power of SS irradiated at 50 kGy. Arrow indicates the position of DPPH line. Figures are the numbers assigned to the studied resonance peaks. (a) 1 mW; (b) 10 mW; (c) 40 mW.

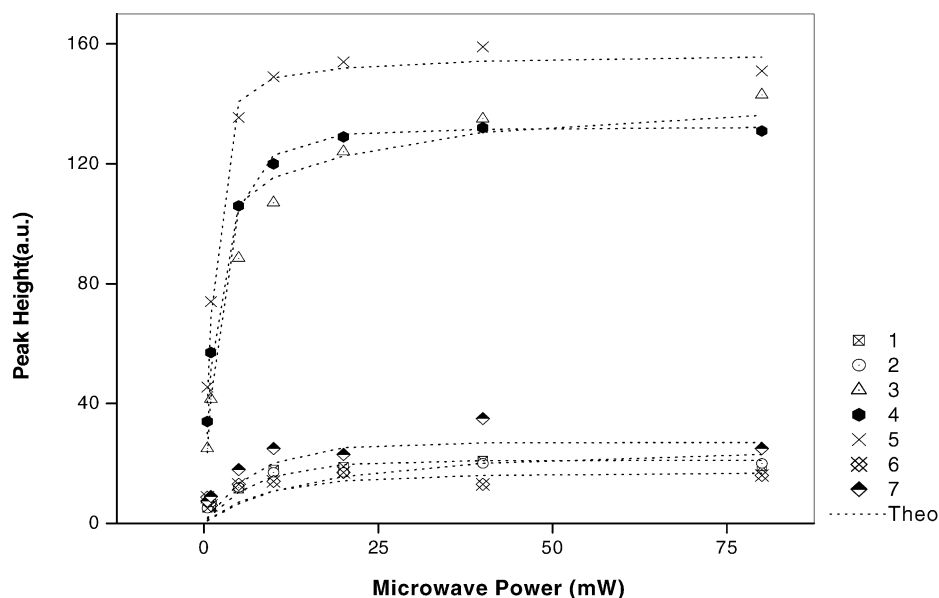


Fig. 2. Variations of the peak heights with microwave power. Symbols: experimental; dashed lines: calculated.

peak heights saturate as inhomogeneously broadened resonance lines at room temperature.

Each radical species is expected to contribute with a different weight to the intensity of a given assigned resonance peak depending on its relative amount, *g* value, hyperfine splitting constant(s) and linewidth. Relative contribution weights of the radical species to the assigned seven resonance peaks calculated from simulation of the spectra recorded at room temperature at a microwave power level of 1 mW (Fig. 6) were used to determine the characteristic parameters relevant to microwave saturation decay at normal and stability conditions and decay at high temperatures. Parameters related with a theoretical function obtained by the sum of four exponentially growing curves of different characteristics (Eq. (1)) associated with the contributing radical species and best fitting to experimental microwave saturation data derived from room temperature spectra, were calculated.

$$I = W_A I_{AO}(1 - e^{-d_A P}) + W_B I_{BO}(1 - e^{-d_B P}) + W_C I_{CO}(1 - e^{-d_C P}) + W_D I_{DO}(1 - e^{-d_D P}) \quad (1)$$

In this equation, *P* is the microwave power in mW; *I*_{AO}, *I*_{BO}, *I*_{CO}, *I*_{DO} are the intensities at saturation; *d*_A, *d*_B, *d*_C, *d*_D are the saturation growth and *W*_A, *W*_B, *W*_C, *W*_D are the relative con-

tribution weights parameters related with the involved radical species assigned as I, II, III and IV, respectively. The results of relative weights and microwave saturation calculations are summarized in Table 1. Variations of the peak heights with applied microwave power calculated using parameters given in Table 1 are represented with their experimental counterpart in Fig. 2.

As seen from the figures given in Table 1, the contributions of the radical species to the studied resonance peaks are very different. Although species I contributes only to the fourth resonance peak, other species contribute to more than one resonance peaks. Species II saturates much faster compared with the other species, however, it dominates the spectra at low microwave power.

3.3. Dose–response curves and dosimetric features of SS

A higher concentration of radicals generated at the same absorbed dose of radiation, indicates a higher sensitivity of the substance toward the type of radiation used. Radiation sensitivity of a substance or mixture is expressed by *G* value, that is, by the number of radicals produced by the absorbed radiation dose per 100 eV. Variations of the heights of the assigned resonance peaks with absorbed gamma radiation dose

Table 1
Parameters for the theoretical sum functions (Eq. (1)) best fitting to experimental microwave saturation data

Radical species	Saturation parameters <i>d</i> (mW ⁻¹)	Relative contribution weights of the radical species to the assigned resonance peaks							Correlation coefficient (<i>r</i> ²)
		1	2	3	4	5	6	7	
I	0.260 (±0.020)	–	–	–	68.9 (±7.2)	–	–	–	0.99
II	0.660 (±0.010)	–	–	104.0 (±5.4)	52.0 (±3.4)	141.0 (±6.0)	–	–	
III	0.140 (±0.003)	21.0 (±2.2)	8.0 (±1.3)	3.0 (±0.8)	8.4 (±2.5)	7.6 (±1.8)	13.0 (±1.9)	27.0 (±3.2)	
IV	0.036 (±0.002)	–	16.0 (±4.1)	31.0 (±4.5)	3.0 (±1.0)	7.5 (±1.3)	4.0 (±1.1)	–	

Figures in bracket represent the estimated error on the relevant parameters.

Table 2
Functions and parameter values best fitting to experimental dose–response data

Peak	Function	Correlation coefficient (r^2)
1	$I(1) = 5.8(1 - e^{-0.044D})$	0.94
2	$I(2) = 4.5(1 - e^{-0.056D})$	0.99
3	$I(3) = 55.4(1 - e^{-0.018D})$	0.99
4	$I(4) = 94.4(1 - e^{-0.013D})$	0.99
5	$I(5) = 126.9(1 - e^{-0.011D})$	0.99
6	$I(6) = 5.5(1 - e^{-0.056D})$	0.94
7	$I(7) = 10.2(1 - e^{-0.024D})$	0.96

D stands for absorbed dose in kGy.

were studied next and the functions of the type given in Eq. (2) were found to describe best experimental dose–response data associated with studied peaks

$$I = I_0(1 - e^{-aD}) \quad (2)$$

in the dose range of 0–50 kGy for SS. In Eq. (2), D stands for the absorbed radiation dose in kGy, a for radiation dose growth parameter and I_0 for intensity at infinite dose. Functions and parameter values best fitting to experimental dose–response data are summarized in Table 2. As seen from the figures given in this table, different radical species with different radiation yields contribute to the ESR spectrum of SS and the radiation yield of the radical species contributing to the peaks assigned as 3, 4 and 5 are much bigger compared to those of other species.

3.4. Stabilities of the radical species at normal and stability test conditions

The stabilities of the radicals produced in irradiated SS were also studied. The decay in time of the peak heights of

Table 3
Decay constants for the contributing radicals calculated from long term signal intensity decay data at normal and stability conditions

Irradiation dose (kGy)	Radical species	Decay constants $k \times 10^5$ (day $^{-1}$)		Correlation coefficient (r^2)
		Normal condition	Stability condition	
50	I	3 (± 1)	9901 (± 285)	0.98
	II	2 (± 1)	7856 (± 200)	
	III	46 (± 5)	11764 (± 325)	0.99
	IV	167 (± 13)	9677 (± 210)	

Figures in parenthesis indicate the estimated error on the relevant parameters. Correlation coefficients: upper (normal); lower (stability) conditions.

the samples irradiated at different doses and stored at normal and stability conditions (75% relative humidity, 40 °C) were found to be independent from the irradiation dose. Thus, the signal intensity decay data obtained for a sample irradiated at a dose of 50 kGy were used to get the decay characteristics of the contributing radicals under both storing conditions. The data relative to the variations of the studied resonance peak heights over a period of 90 days for samples stored both at normal and stability conditions were found best fitting to the sum of four exponentially decaying functions of different weight and of different decay constants as given in Eq. (3).

$$I = W_{A0}e^{-k_A t} + W_{B0}e^{-k_B t} + W_{C0}e^{-k_C t} + W_{D0}e^{-k_D t} \quad (3)$$

In the last equation, t ; W_{A0} , W_{B0} , W_{C0} , W_{D0} ; k_A , k_B , k_C , k_D stand for the time elapsed after the stopping of irradiation, the initial signal intensities or initial contribution weights and decay constants of the contributing radical species, respectively. This result which agrees with the microwave saturation data was considered, once more, as the justification of the presence of more than one radical species of different decay characteristics contributing to the formation of the ESR spectra of

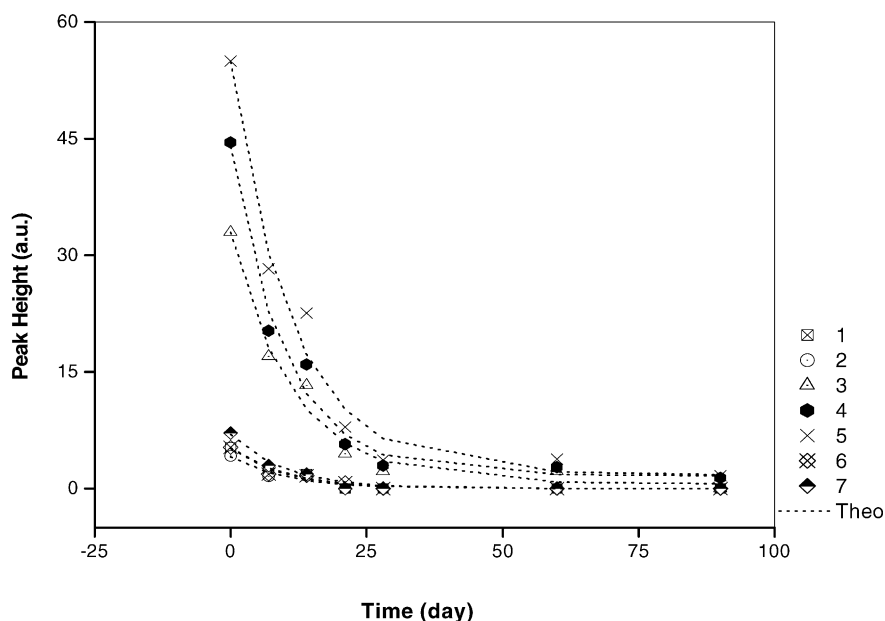


Fig. 3. Variations in signal heights of SS irradiated at a dose of 50 kGy and stored at stability conditions over a period of 90 days. Symbol: experimental, solid lines: theoretical.

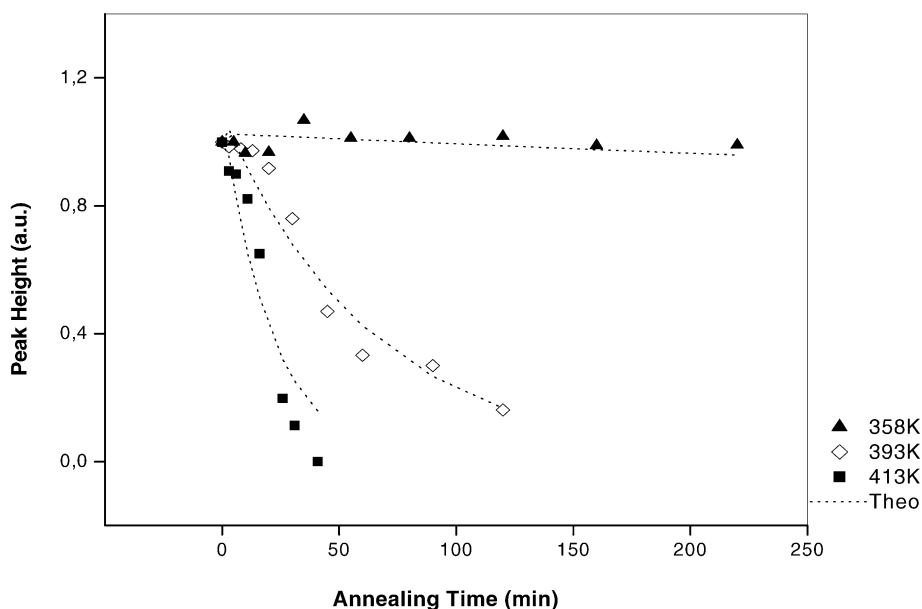


Fig. 4. Signal intensity decay results for peak 4 of a sample irradiated at a dose of 50 kGy and annealed at three different temperatures (▲ 358 K), (◇ 393 K), (■ 413 K) for different times.

irradiated SS. The decay constants derived from this study are summarized in Table 3 and theoretical decay results calculated using these parameters are given together with their experimental counterparts, in Fig. 3 for the decay at stability conditions. As is expected, the decays of the contributing radical species were much faster under stability conditions. Peak heights of irradiated SS decreased $\sim 90\%$ in the first 20 days after stopping irradiation when stored in stability conditions. Although, all radical species decay with similar decay constants at stability conditions, they decay differently at normal conditions. Species IV is very unstable even at normal conditions compared to the other species.

3.5. Variations of the peak heights with temperature

A variable temperature study relative to the variations of the peak heights with temperature were performed in the range of 140–295 K and 295–400 K. Cooling the sample down to room temperature caused reversible increases in the resonance peak heights likely due to classical paramagnetic behaviours of the contributing radical species. Warming the sample above room temperature produced no significant changes in the heights of the observed peaks contrary to the preliminary results obtained in our laboratory for other sulfonamides such as sulfanilamide, sulfathiazole and sulfafurazole. This is interpreted as originating from high stabilities of the radical species produced in irradiated SS likely due to higher cage effect of SS lattice compared with other sulfonamides.

3.6. Radical decays in annealed samples

Radical decay rates depend on the nature of the matrix containing radicals and annealing is a constant process with

local diffusion of radicals and molecules in some softening of defects or irregularities [22]. Increase in temperature accelerates the decays of the radicals and the higher is the temperature the higher is the decay rates. In fact, it was also the case for SS. Four radical species responsible for ESR spectrum of irradiated SS are expected to have different decay characteristics depending on the sample temperature. Signal intensity decay results obtained for peak 4 of a SS sample irradiated at a dose 50 kGy and annealed at different temperatures for different times are given Fig. 4 as an example of these variations. Similar decay result were obtained for other resonance peaks, but they were not given here to save space. Experimental peak height decay data obtained for samples annealed at different temperatures were used to calculate the decay constants of the contributing radicals at the annealing

Table 4
Decay constants at different temperature for the radical species contributing to the ESR spectra of SS irradiated at a dose of 50 kGy

Annealing temperature (K)	Radical species	Decay constant [$k \times 10^5$ (min^{-1})]	Correlation coefficient (r^2)
358	I	9 (± 1)	0.98
	II	7 (± 1)	
	III	69 (± 4)	
	IV	31 (± 3)	
393	I	1436 (± 115)	0.99
	II	1234 (± 80)	
	III	2755 (± 180)	
	IV	1257 (± 105)	
413	I	4536 (± 185)	0.99
	II	3547 (± 155)	
	III	7215 (± 220)	
	IV	5390 (± 205)	

Figures in parenthesis indicate the estimated error on the relevant parameters.

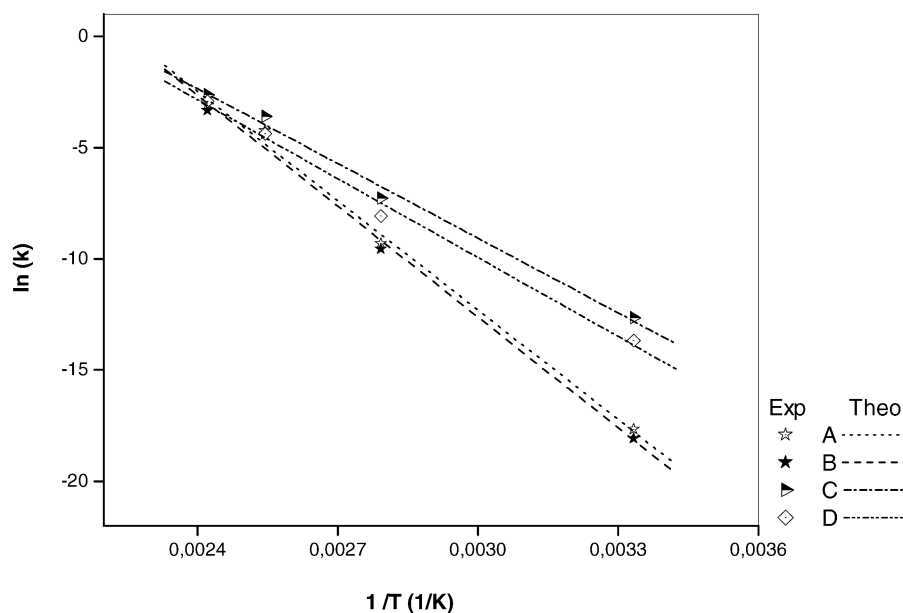


Fig. 5. Arrhenius plot constructed for SS irradiated at a dose of 50 kGy. Symbols: experimental, dashed lines: theoretical.

temperatures assuming that radicals follow a first order kinetics as given by Eq. (3). Four radical species of different decay constant decaying with assumed kinetics were found to fit best the experimental signal intensity decay data. Dotted lines in Fig. 4 show the theoretical curves obtained by this procedure. Decay constants calculated for radicals contributing to the formation of the ESR spectra of the SS irradiated at a dose of 50 kGy and annealed at three different temperatures are summarized in Table 4. An Arrhenius plot was also constructed using calculated decay constants to determine the activation energies of the contributing radical species and the graph given in Fig. 5 was obtained. The activation energies calculated from the slopes of the straight lines given in Fig. 5 are summarized in Table 5.

3.7. Proposed radical species and spectra simulations

Excited molecules are produced both directly and through radical–cations neutralization reactions [23]. They may decompose to radicals by rupture of chemical bonds. However, radicals which are molecular fragments, can not diffuse in solid matrices due to cage effect and therefore, immediate germinate termination reactions are possible [22]. Excited

molecules and, as a result, radicals are localized along the track in region of high local concentration. SO_2 is the most sensitive group to radiation in SS molecule due to its high electrophilic feature. Therefore, radicals with unpaired electrons localised on SO_2 group is expected to be likely produced upon irradiation of SS as in the case of sulphur containing compounds [24–30]. These radicals exhibit no hyperfine structure and they have g tensor of orthorhombic symmetry with an average value varying between 2.0037 and 2.0059 [24–26]. Experimental g values determined in the present work for resonance peaks of the gamma irradiated SS fall into this range. Consequently, we believe that SO_2^- ionic radical (hereafter radical I) and molecular ionic fragment $[\text{O}=\text{S}=\text{O}]^-$ (hereafter radical II) are the responsible magnetic units from the three resonance peaks appeared at the middle of the ESR spectra of gamma irradiated SS. Radical I and II produced in irradiated crystalline powder of SS are randomly oriented. However, the motion of radical II is restricted, in large extent, due to the big group attached to it, so that it gives rise to powder spectra with principal g values varying between $g_{xx} = 2.0022$ – 2.0031 , $g_{yy} = 2.0015$ – 2.0098 and $g_{zz} = 2.0058$ – 2.0066 [25,26]. As for SO_2^- ionic radical or radical I, its motional freedom is high due to very weak steric effect experienced by this radical and, as a result of this, it gives rise to a single resonance line of average spectroscopic g factor varying between 2.0037 and 2.0059 [24,26].

Simulation calculations were performed to support the idea put forward with the radical species responsible from the observed experimental seven peaks ESR spectra of gamma irradiated SS and to determine correct spectroscopic parameters of the contributing radical species assuming the presence of four radicals, exhibiting isotropic and axially symmetric g tensors. Room temperature experimental signal intensity data

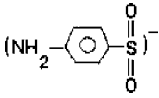
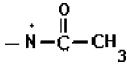
Table 5

Activation energies calculated from the decay constants derived for samples irradiated at a dose of 50 kGy

Radical species	Activation energy (kcal/mol)	Correlation coefficient (r^2)
I	32.5 (± 1.5)	0.99
II	32.9 (± 1.7)	0.99
III	22.2 (± 1.3)	0.99
IV	23.4 (± 1.3)	0.99

Figures in bracket indicate the estimated error on the relevant energy.

Table 6
Calculated spectroscopic parameters for contributing radical species produced in irradiated SS

	Radical species	Spectroscopic parameters		
		g Factor	Line width (G)	Hyperfine splitting A (G)
I	$(\text{SO}_2)^{\cdot -}$	2.0052 (± 0.0002)	1.21 (± 0.20)	–
II		2.0092 (± 0.0002)	2.15 (± 0.02)	–
		2.0031 (± 0.0002)		
III		2.0033 (± 0.0002)	4.25 (± 0.20)	19.7 (± 0.2)
IV	$\dot{\text{C}}\text{H}_3$	2.0040 (± 0.0002)	3.50 (± 0.20)	8.6 (± 0.2)

obtained for a sample irradiated at a dose of 50 kGy were used as input to carry out the simulation calculations. The results of these calculations are summarized in Table 6 and theoretical spectrum derived from the parameter values given in this table are presented in Fig. 6 with its experimental counterpart. The spectra of the contributing radical species (I–IV) are also given in the same figure. The line width of radical III is large compared with other radical species and radicals I and II dominate together ESR spectrum. As seen the agreement between experimental and theoretical spectra is fairly good which indicates that the model based on four radical species of different characteristic features explains well the experimental ESR spectra of irradiated SS.

Gamma irradiated frozen aqueous solutions of sulphacetamide have been examined in the literature [31] using ESR

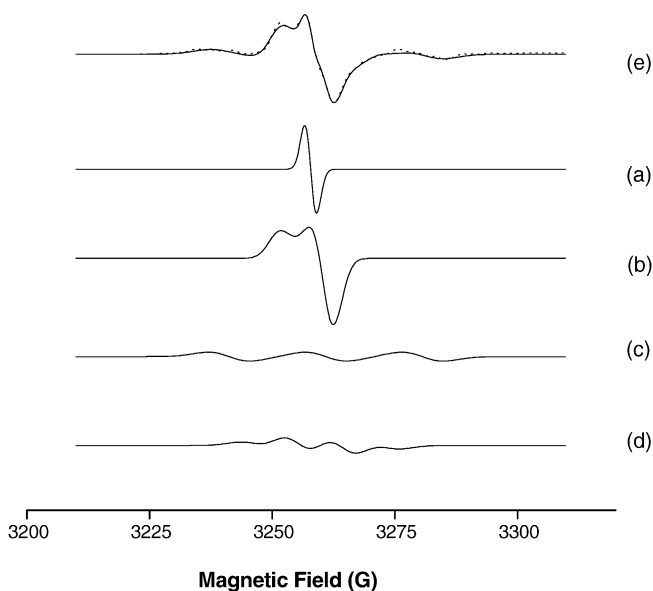


Fig. 6. Experimental and calculated ESR spectra for SS irradiated at a dose of 50 kGy. (a–d) Calculated spectra for radical species I–IV, respectively. (e) Experimental and calculated sum spectra. Solid line: theoretical, dashed line: experimental.

to look for possible intermediates in the radiation degradative pathway. The examination has been conducted at 77 K and a single resonance line centered at $g = 2.0075$ was reported for a sample annealed to 120 K. This value falls into the g value range reported in the present work for gamma irradiated solid SS (Table 6).

3.8. IR results

IR spectroscopy was thought may be a complementary technique to elucidate the types and structures of the radiation induced radical species and, as a result, FT-IR spectra of both unirradiated and 50 kGy gamma irradiated SS were recorded at room temperature. However, significant differences in IR bands attributable to any intermediates created by radiation were not observed between these spectra. Difference spectra were also constructed using IR spectra of unirradiated and irradiated samples of same mass but still meaningful results were not obtained. This was considered to be likely due to the fact that the amounts of the radiation induced intermediates were very small not creating any detectable changes in the IR bands originating from undamaged molecules. This result was considered as correlating with relatively small G value (0.1) reported in the present work for gamma irradiated SS by ESR technique.

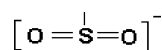
4. Conclusions

Samples of SS irradiated at room temperature exhibited a complex ESR spectra consisting of seven resonance peaks which saturated as inhomogeneously broadened resonance lines in the studied microwave power range (1–80 mW). However, radiation yield of SS was very small ($G = 0.1$) compared with those reported for sulfonamide solutions (G varies in the range of 3.5–5.1), but it falls into the range of the G values reported for solid sulfonamides (0.15–0.6) [31,32]. This difference in G values was believed to originate from hydrated electron (e_{aq}^-) and hydroxyl radicals

(•OH) produced in large amount as radiolytic intermediates in irradiated aqueous solutions of sulfonamides. Although, the sensitivity of solid SS to gamma radiation was not high, the detection and discrimination of unirradiated SS from irradiated one turned out to be possible even at low radiation doses. Most sensitive subgroup of SS molecule to radiation, that is SO_2 , was believed to be at the origin of the observed main resonance lines of irradiated SS. Therefore, tentative ionic radical species that is radicals I and II,

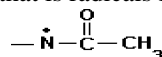
$(\text{SO}_2)^-$

(I)



(II)

were assumed to be produced upon irradiation giving rise to isotropic and axially symmetric ESR spectra. In addition to these radical species, that is radicals I and II,



(III)



(IV)

radicals III and IV were also found to be involved in the irradiated SS after simulation calculations. Radical III is formed after the break of N–Na bond and it has hyperfine splittings as the unpaired electron is localized on nitrogen atom. However methyl radical ($\overset{\cdot}{\text{C}}\text{H}_3$) is formed after the break of C–C bond and its unpaired electron is expected to be localized on carbon atom. It has four peaks with 1:3:3:1 relative weight due to the methyl hydrogens.

The radical species were quite stable at room and high temperatures. Radical decay data obtained for samples stored at room temperature over a period of 90 days indicated that ESR signal could be detected even after a storage period of several months in irradiated SS. Thus, it was concluded that irradiated SS could be distinguished from unirradiated one by ESR spectroscopy even long after the irradiation. Weak sensitivity of solid SS to gamma radiation and rapid decay of the radical species at stability conditions indicate that SS can be efficiently sterilized by radiation and that ESR spectroscopy could be used as a potential technique in monitoring the radiosterilization of SS and/or drug delivery systems containing SS as active ingredient. However the results show that, solid SS do not present the features of a good dosimetric material due to its very small radiation sensitivity ($G = 0.1$), although radicals produced in it have relatively high decay activation energies (Table 5). Therefore, it can not be used as an efficient dosimetric material.

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