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# DSC and spectroscopic studies of disulfiram radiostability in the solid state

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**Abstract** The effect of ionising radiation on the physico-chemical properties of disulfiram (Antabuse, Esperal, bis-diethylthiocarbamoil disulphide) has been studied by DSC, FTIR, EPR, MS, TLC and HPLC. Sterilisation was carried out in the solid state, at room temperature and normal air humidity using the electron beam of 9.96 Mev from accelerator. All the measurements were made simultaneously for the irradiated and nonirradiated substance. It has been found that the drug studied in solid phase when subjected to an electron beam corresponding to the irradiation in the doses 10–100 kGy shows the presence of free radicals (EPR), and a change in colour from white to pale green-grey that disappears after solution in water or methanol. After the irradiation with the dose of 100 kGy, its melting point and enthalpy slightly decreased. Also the content of the active substance decreases (HPLC −1.5%, UV −3.6%, iodometric titration method −2.7%) and trace amounts of the radiolysis products appear (HPLC). The substance irradiated with the doses 10–50 kGy does not show changes in the melting point, in the content and presence of the radiolysis products. The EPR results have shown that free radicals disappear after about a year and the discolouring disappears with them. The results of this study have shown that disulfiram can be subjected to sterilisation by irradiation with no deterioration of its physico-chemical properties, but a long time of storage needed to remove free radicals and discolouration questions the economic justification for this type of sterilisation.

**Keywords** Disulfiram · Radiosterilization · Stability

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## Introduction

Starting from the 1980s, increasing interest has developed in radiation sterilisation [1–5]. Beta (using electron beam) or gamma irradiation is an alternative and very attractive method for sterilization of pharmaceutical substances or medical devices [6, 7]. The main difference between electron-beam and gamma-radiation is the dose. The same irradiation dose using gamma radiation can be obtained in several hours, whereas electron beam radiation requires only a second [8]. The sterilisation procedures using irradiation have many advantages, such as high efficiency, no temperature requirements, possibility of sterilisation in packages but on the other hand, the ionisation radiation applied can damage a given drug being sterilised [9] so the effect of sterilisation radiation should be checked before its application. One of the most widely used methods of analysing the drugs purity and possible changes occurring during processing of drug is the differential scanning calorimetry (DSC) [10–12]. The aim of this study was to check the effect of radiation sterilisation on disulfiram in solid phase by DSC and spectroscopic methods.

Disulfiram (Antabuse, Esperal, bisdiethylthiocarbamil disulphide) is a well-known therapeutic drug applied in treatment of alcoholism to prevent drinking alcohol by producing unpleasant side effects, such as headaches,

disturbances of the circulatory system performance, disturbances of the alimentary tract performance, dysmnesia, allergic reactions, and others. These symptoms appear as a result of inhibition of alcohol oxidation by disulfiram and accumulation of acetic aldehyde leading to organism poisoning. Disulfiram is used in the form of tablet for oral use and for hypodermic implantations. The latter, together with the other drug formulations, such as injections, infusions or eye drops, must be sterile. Their sterilisation has been ensured by different methods including the use of hot saturated vapour, dry air, ethylene oxide or filtration.

According to the literature [13], small doses of irradiation <1 kGy can be safely applied, however, such small doses do not guarantee full sterilisation and the European norm recommends for this purpose a dose of 25 kGy [14]. In view of the above, this study was undertaken to check the effect of greater doses (10–100 kGy) of ionising radiation on the physico-chemical properties of disulfiram.

## Materials and methods

### Materials

Disulfiram, bis(diethylthiocarbamyl) disulphide, molecular formula $(C_2H_5)_2NCSS_2CSN(C_2H_5)_2$, molecular weight 296.52 g $mol^{-1}$ (LOT 005/02 WZF "Polfa" S.A, Poland) (Fig. 1). The compound satisfied the pharmacopoeia requirements.

### Exposure to irradiation

The samples of disulfiram (approximately 0.5 g) were placed in colourless glass vials of 4-mL capacity and closed with plastic stoppers. They were subjected to irradiation at doses of 10.0, 25.6, 53.4 and 103.6 kGy using a linear electron accelerator LAE 13/9, the energy of electrons was 9.96 MeV and the average beam current was 6.2 μA. The nominal doses were measured by calorimeter [15]. The electron energy was measured with the use of an aluminium wedge. The irradiation was performed at room temperature, on conveyor and its duration varied from 2 to 8 s, depending on the dose. The irradiation with subsequent doses was performed after 30 min breaks needed to ensure that the sample temperature did not exceed 30 °C. The dose distribution in the conveyor was homogeneous in the confidence interval of ±10%.

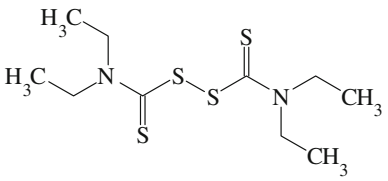


**Fig. 1** The structural formula of disulfiram

### Organoleptic analysis

The substance was examined before and after irradiation with respect to the appearance, colour, smell and clarity of the solution obtained by dissolving it in methanol. All the experiments were performed in accordance with Pharmacopoeia Polonica [16].

### Differential scanning calorimetry (DSC)

Measurements were performed on an apparatus DSC-204 made by Netzsch. Samples of 3 mg were closed in aluminium crucibles with pierced lids. Before measurements, the samples were thermally equilibrated at 20 °C for 5 min, and the measurements were performed at the heating rate of 5 °C $min^{-1}$, in helium atmosphere (40 mL $min^{-1}$). For each sample, three independent measurements were performed and the results were averaged. The data were analysed using TA Netzsch program. For determination of enthalpy values characterising phase transitions, a linear or a tangent-sigmoidal baseline was used.

### Thin layer chromatography (TLC)

The compound studied in acetone solution of a 2% concentration was injected by a Hamilton injector in the amounts of 10, 50, 100 and 150 μL onto the starting points, then they were dried in air stream at room temperature and placed in chromatographic chambers, where they were developed over 16 cm in different systems of solvents (mobile phase) and two stationary phases.

#### *Mobile phases*

Hexane:ethyl acetate (7:3); hexane:butyl acetate (7:3) [17]; methanol:25% $NH_4OH$ (100:1.5) [16]; chloroform:methanol (9:1) [18]; cyclohexane:toluene:diethylamine (75:15:10) [18] and our other modifications: *n*-butanol:25% acetate acid:ethanol (10:5:2); *n*-butanol:25% acetic acid:water (20:4:9); *n*-butanol:15% ammonium acetate:ethanol (2:2:1); ethyl ether:ethanol:water (5:4:1); 1-propanol:water (8:1); dioxane:ethanol:acetone:pentanol (25:15:15:2).

#### *Stationary phases*

Silica gel 60 $F_{254}$
Silica gel HP TLC 60 $F_{254}$

### High-performance liquid chromatography (HPLC)

The HPLC system consisted of a Waters Model 616 solvent pump system equipped with a Photodiode Array UV–VIS Waters 996 detector set at 254 nm. Chromatographic separation was performed using a Waters Symmetry C18 reverse phase column (3.9 mm × 250 mm, 2.5 µm particle size). The mobile phase consisted of water–acetonitrile (50:50 v/v), the rate of flow was 1.5 mL $min^{-1}$. The separation was conducted at room temperature. The precision of the HPLC method was characterised by relative standard deviation of 1.96%. The quantification limit was 0.55 mg $L^{-1}$, and the limit of detection was 0.18 mg $L^{-1}$.

### Ultraviolet spectrophotometry (UV)

The solutions were prepared by dissolving the substance in methanol solution to obtain concentrations 0.001% m/v. The solutions were studied using UV/VIS PERKIN ELMER Lambda 20 spectrophotometer, in 1 cm cuvettes in the range 200–400 nm, using a solvent as a blank.

### Infrared spectroscopy (FTIR)

The FTIR spectra were obtained using FTIR/Raman spectrometer IFS66 (Bruker Optics). The spectrometer was equipped with a Globar IR source, KBr beam splitter and a DTGS detector. For each spectrum, 512 scans were taken with the resolution of 1 $cm^{-1}$. The spectra were recorded in transmission mode at room temperature, 65, 70, 75 and 80 °C in the range 600–4000 $cm^{-1}$ using KBr as a blank.

### Raman spectroscopy

The Raman spectra were recorded on the FT-Raman module of the same FTIR/Raman spectrometer (Bruker IFS66). The beam-splitter was quartz and the excitation source was Nd-YAG laser (the laser power 300 mW), which emitted a continuous-wave laser energy at a wavelength of 1064.6 nm (9393.5 $cm^{-1}$). The recording was performed in the range 3500–100 $cm^{-1}$ at a resolution of 4 $cm^{-1}$ (1024 scans). All the measurements were performed at room temperature.

### Mass spectrometry (MS)

Mass spectra of the compounds studied were taken before and after irradiation of disulfiram with a dose of 103.6 kGy on an AMD 604 spectrometer, in standard conditions, i.e. at the voltage of 70 V, so with electrons of the energy of 70 V.

### Electron paramagnetic resonance (EPR)

The EPR experiments were carried out for non-irradiated and irradiated samples, in standard EPR quartz sample tubes from Wilmad. The measurements were performed using a Bruker EPR EMX-10 spectrometer working at 9.4 GHz (X-band) at room temperature (293 K) equipped with a rectangular cavity (ER 4102ST; Bruker).

## Results and discussion

According to the organoleptic analysis of disulfiram performed before the sterilisation by irradiation, the compound was a white loose powder without smell. When dissolved in methanol, it gave a clear colourless solution. After irradiation of the powdered compound with e-beam corresponding to the doses of 10.0, 25.6, 53.4 and 103.6 kGy, the white colour changed into pale grey-green (the dose of 10.0 kGy) to grey-green (103.6 kGy). The methanol solutions ($c = 0.1\%$) prepared from the discoloured substance remained clear and transparent after irradiation with all the doses studied, which could suggest that the discolouration was not a result of the formation of coloured products of decomposition, but was due to the presence of coloured free radicals generated by ionising radiation.

Therefore, a test was made to verify this thesis, at first by DSC and TLC measurements. The DSC method is known to show a decrease in the melting point of the compound studied if it is contaminated with the radiolysis products [19–23].

According to DSC measurements for the substance irradiated with 53.4 kGy, the melting point of the irradiated substance is the same as that of non-irradiated and is 71.3 °C (Fig. 2). After irradiation with 103.6 kGy, a small decrease by 0.2 °C in the melting point was noted, to

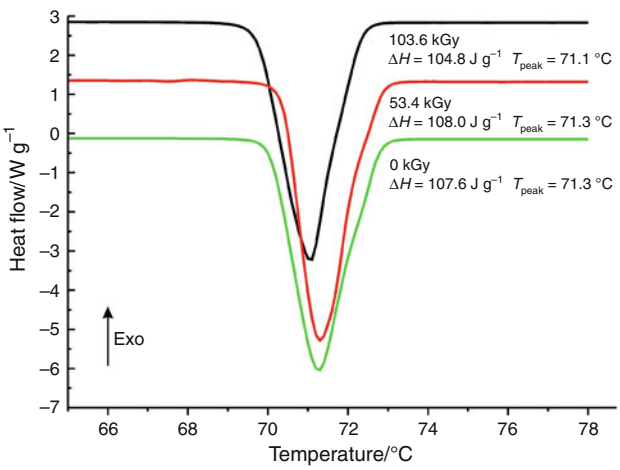


**Fig. 2** DSC curves of disulfiram before and after irradiation

71.1 °C. Also in the melting enthalpy ($\Delta H$), small variations were observed. For the initial substance, $\Delta H$ was 107.6 J $g^{-1}$, and for the substance irradiated with a dose of 53.4 kGy it increased by 0.4–108.0 J $g^{-1}$, which is within the error of the method. For the substance irradiated with a dose of 103.6 kGy, the enthalpy decreased by 3.0 J $g^{-1}$, which is significant and together with the decrease in the melting point by 0.2 °C these changes can suggest the beginning of decomposition of the substance studied. The results indicate the lack of impurities (e.g. products of

**Table 1** Results of determination of disulfiram by the UV spectrophotometric method, by the method recommended by pharmacopoeia before and after sterilisation by irradiation

| Parameter | Dose/kGy | | | | | |
|---|---|---|---|---|---|---|
| | 0 | | 10 | 25.6 | 53.4 | 103.6 |
| UV-spectrum | $\lambda_{max}$ | $a_{1\ cm}^{1\%}$ | No changes | No changes | No changes | No changes |
| | 220 nm | 730 | | | | |
| | 250 nm | 450 | | | | |
| | 280 nm | 376 | | | | |
| Absorbancy at $\lambda_1 = 220$ nm | 0.880 | | 0.901 | 0.885 | 0.877 | 0.848 |
| Content (%) | | | | | | |
| UV method | 100.0 | | 102.4 | 100.6 | 99.7 | 96.4 |
| Iodometric method | 100.0 | | 102.0 | 100.8 | 100.1 | 97.3 |
| Differences in contents [%] | | | | | | |
| UV method | – | | +2.4 | +0.6 | −0.3 | −3.6 |
| Iodometric method | – | | +2.0 | +0.8 | +0.1 | −2.7 |

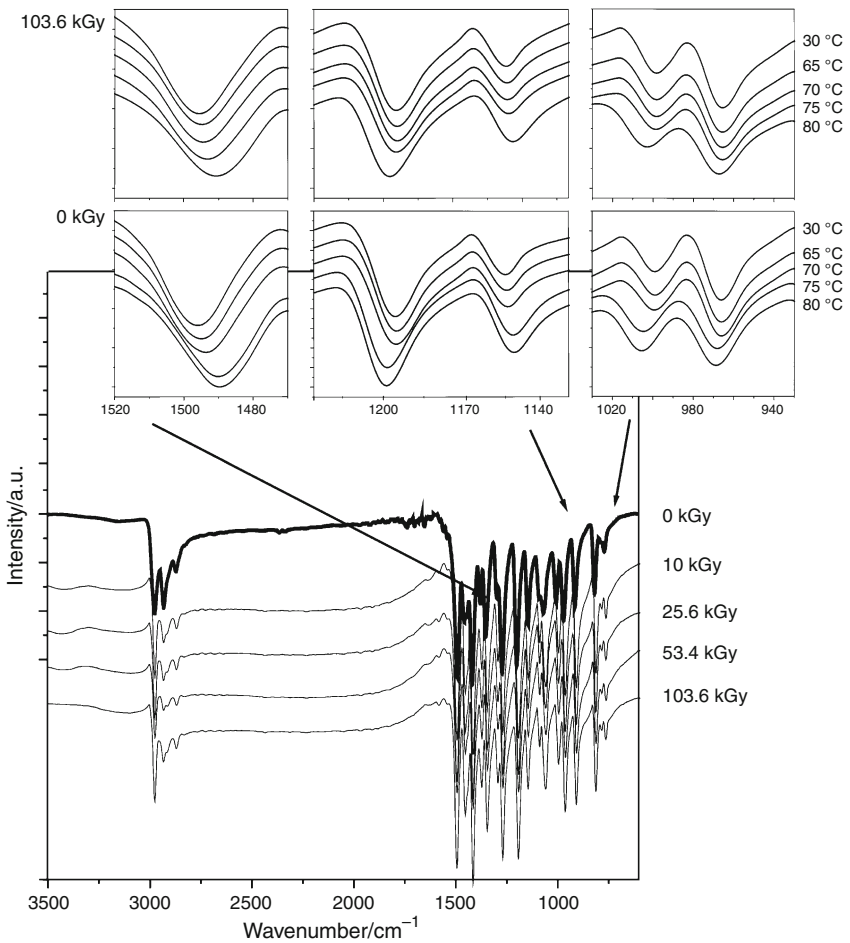


**Fig. 3** FTIR spectra of disulfiram before (0 kGy) and after irradiation (103.4 kGy) and temperature dependences of selected bands

decomposition or radiolysis) in the substance irradiated with doses lower than 103.6 kGy, also the TLC results did not suggest the presence of radiodegradation products.

The chromatographic TLC analysis of the samples before and after irradiation did not show the presence of impurities in the initial sample or the appearance of the decomposition or radiolysis products in the samples irradiated with all the doses applied, even in the presence of 150 µL of a 2% solution of disulfiram.

Assuming that the sensitivity of the TLC method is limited, the substance was subjected to the spectrometric methods UV, IR and MS.

The UV spectra of the disulfiram irradiated with doses up to 53.4 kGy analysed in the range 200–350 nm, did not show any changes in absorbency at the absorption maxima ($\lambda_1 = 220$ nm, $\lambda_2 = 250$ nm and $\lambda_3 = 280$ nm) with respect to that of non-irradiated substance. Only for the sample irradiated with 103.6 kGy, a decrease in absorbency at $\lambda_1$ was observed, indicating a decrease in the content by about 3% (Table 1). Similar results were obtained when determining the content of disulfiram by the iodometric titration, method recommended in the pharmacopoeia [16].

The FTIR spectra of disulfiram irradiated with all the doses are presented in Fig. 3. The selected characteristic bands at 1497 $cm^{-1}$ (C–H sym. deformation vibrations), 1195 $cm^{-1}$ (C–H skeletal vibrations), 1150 $cm^{-1}$ (C–C rocking vibration), 998 $cm^{-1}$ (C–C vibrations) and 966 $cm^{-1}$ (C–H rocking vibrations) were fitted using Gaussian profiles. The temperature dependences for these bands are presented in Fig. 4 The characteristic bands of disulfiram irradiated with all the doses did not show significant changes ($\Delta v < 1$ $cm^{-1}$) with respect to that of non-irradiated substance. Somewhat larger changes (but $\Delta v$ not exceeding 7.5 $cm^{-1}$) were observed during heating. This effect was however weaker for samples irradiated the largest dose of radiance. The small changes in the intensities of the absorption bands were also noted.

The Raman spectra of disulfiram irradiated with all the doses and recorded in the range 100–3500 $cm^{-1}$ also did not show significant changes with respect to that of non-irradiated sample, although small changes in the intensities of the main absorption bands were noted (Fig. 5).

The mass spectra of the irradiated and non-irradiated disulfiram also did not show significant differences (Fig. 6, Table 2), all the spectra contained the molecular ion $[M]^+$ at *m/z* 296.2 and the main ion at *m/z* 116.1. Apart from them, in all the MS spectra an additional ion was observed at m/z 359.1, most probably due to a production impurity or a product of decomposition (e.g. disulfiram oxidation). The ions observed in the mass spectra had the same masses and the same abundances except for the sample irradiated with the dose 103.6 kGy, for which the following observations were made.

- After irradiation, the abundance ratio of the peaks at 148.1 and 149.1 changed.
- A new peak at *m/z* 244 in the mass spectra of the substance after irradiation appeared. The abundance of the peak was very small (2–3% of relative abundance), and the peak can correspond to a product of mass decomposition of disulfiram or from mass fragmentation of the impurity of a mass 359.1.

To sum up, the results obtained by UV, IR and MS clearly pointed to the appearance of radiodegradation symptoms near the dose of 100 kGy. To confirm this conclusion a HPLC analysis was made, whose results

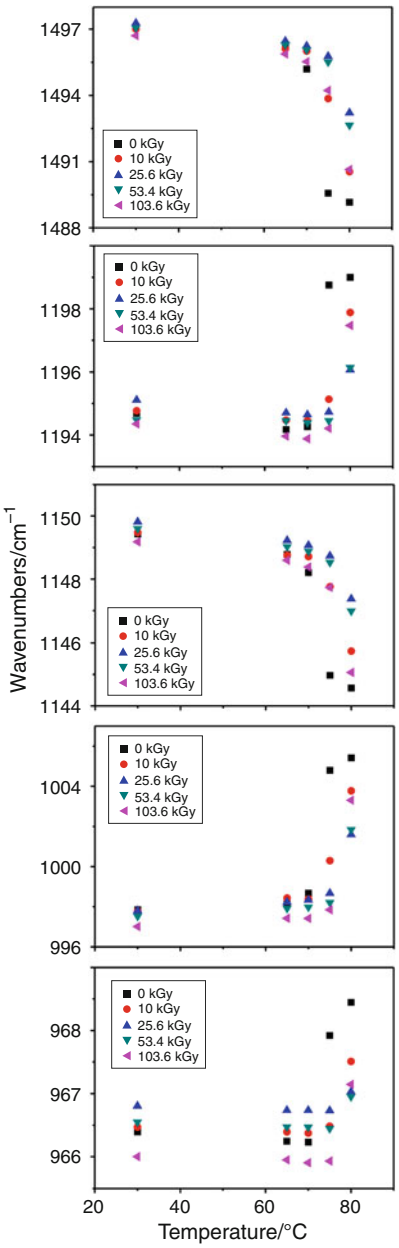


**Fig. 4** Temperature dependence of the selected characteristic bands

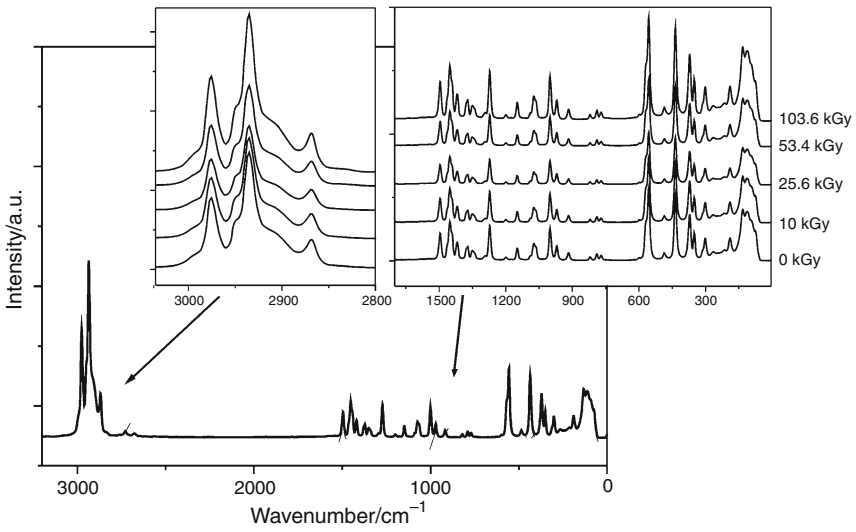


**Fig. 5** Raman spectra of disulfiram before and after irradiation

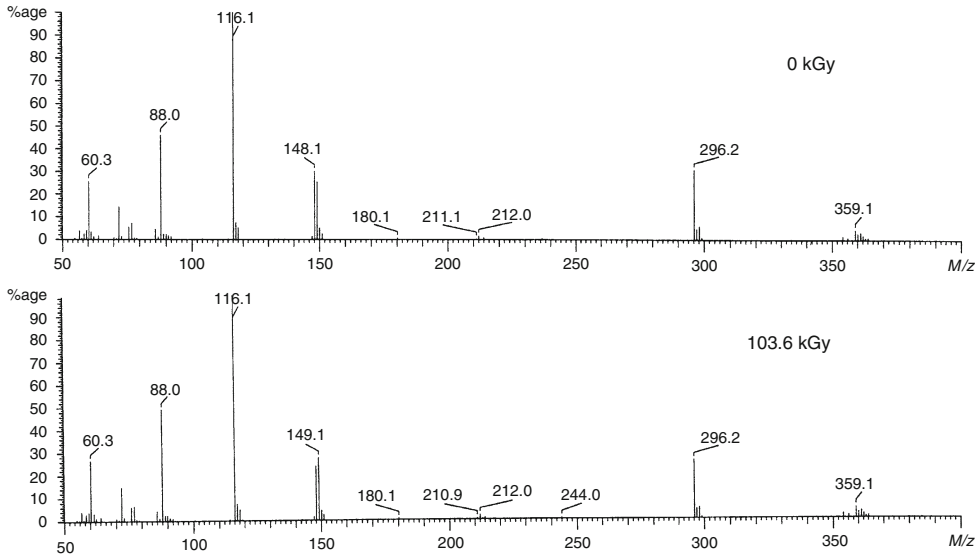


**Fig. 6** MS spectrum of disulfiram before and after irradiation

indicated that the initial substance was contaminated with a compound of $t_R = 19.62$ (Fig. 7). Most probably, it is the compound detected in the mass spectrum at *m/z* 359.1. The HPLC data for the sample irradiated with the dose of 103.6 kGy proved the presence of two products of radiolysis, characterised by $t_R = 17.62$ and 21.90 min, and a decrease in the content of disulfiram by about 1.5%. In the samples irradiated with the doses 10–53.4 kGy, no radiolysis products were detected besides the contaminating substance characterised by $t_R = 19.62$ min. The radiolysis products and the contaminant observed occurred in trace amount, which is supported by the fact that they were not detected by the TLC method.

To sum up, the results of the studies performed have confirmed that disulfiram subjected to sterilisation with doses <100 kGy does not show the presence of radiolysis products. Only after its irradiation with 100 kGy, trace amounts of two products of radiolysis appear and it is highly unlikely that they are responsible for the sample discolouration. A more probable hypothesis is that the discolouration is due to the coloured free radicals. To verify this hypothesis, the irradiated and non-irradiated disulfiram was subjected to EPR study. The EPR results have shown that free radicals appear in the samples of disulfiram irradiated with both low (25.6 kGy) and high (103.6 kGy) doses, but they are not detected in non-irradiated samples (Figs. 8, 9).

The concentration of the free radicals formed matched the standard values for the doses applied [5, 24, 25] and was $6.05 \times 10^{14}$ spin g$^{-1}$ for the sample irradiated with 25.6 kGy.

EPR spectrum of disulfiram after irradiation shows a broad anisotropic signal of hyperfine interaction (Figs. 8, 9). The characteristic *g*-factor of this signal is $g_1 = 2.04$

**Table 2** Comparison of the MS spectra of disulfiram before and after irradiation

| Parameter | 0 kGy | 103.6 kGy |
|---|---|---|
| Molecular ion $[M]^+$ | 296.2 | 296.2 |
| Parent ion | 116.1 | 116.1 |
| Fragmentation ions | 88.0 | 88.0 abundance changes |
| | 148.1 | 149.1 after |
| | 60.3 | 60.3 sterilization |
| | | 244.0 new (low abundance) ion appearing after sterilization |

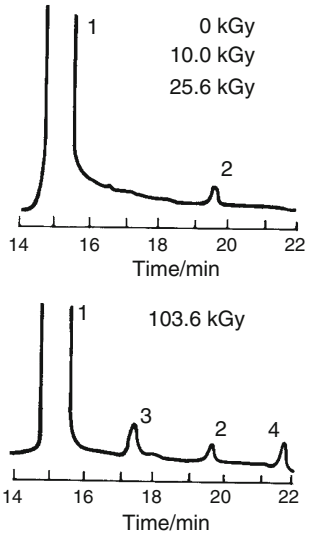


**Fig. 7** Typical HPLC chromatograms of disulfiram before and after irradiation: *1* disulfiram; *2* impurity; *3*, *4* products of radiolysis

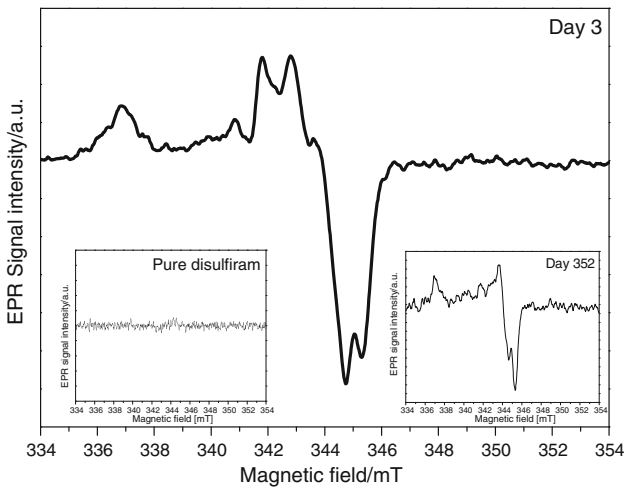


**Fig. 8** EPR spectra of disulfiram before and after irradiation (25.6 kGy)

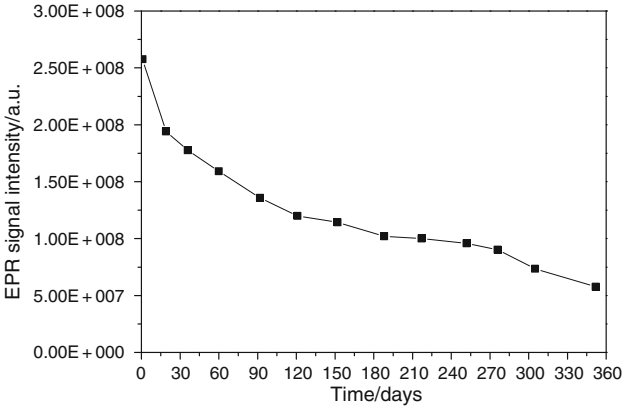


**Fig. 9** Decay of radicals upon storage (25.6 kGy)

and $g_2 = 2.0056$. The functional group in disulfiram is ethyl group $–CH_2–CH_3$. Literature does not bring information on the earlier EPR studies of disulfiram, but it is possible to gain some data on the possible types and formation of free radicals in this class of chemical compounds (RSSR). In disulfiram, the radical is formed at the same position as in the other compounds from the group of tetraalkylthiuram disulphides.

The measurements of the free radicals life-time showed that their concentration slowly decreases with time, so that some of them (about 22% of the amount observed directly after the irradiation) are still present after a year from the irradiation. With decreasing number of free radicals the grey-green colour of the irradiated samples was observed to disappear, the white colour reappeared after about 16 months. This observation supports our hypothesis that the change in the substance colour was related to the presence of free radicals and not to the appearance of the radiolysis products.

## Conclusions

Results of the study have permitted drawing the following conclusions. Disulfiram *in substantia* irradiated with the dose of 25.6 kGy recommended for sterilisation shows no significant changes in:

- The course of the UV, IR, MS spectra and DSC curve,
- Chromatographic purity (TLC, HPLC),
- Melting point and content.

However, the irradiation produces:

- A faint specific smell,
- Grey-green colour,
- The appearance of a medium-intensity EPR signals testifying to the appearance of free radicals.

Only after irradiation with a dose of 103.6 kGy, the following changes can be observed:

- Small changes in the MS, UV and IR spectra (a decrease or increase in intensity of certain bands),
- Significant changes in the DSC curve (a shift proving a decrease in the melting point) and EPR spectrum (an increase in intensity),
- The appearance of the two products of radiolysis evidenced by HPLC,
- A decrease in the content determined by UV method (−3.6%), by the method recommended in the pharmacopoeia (−2.7%) and by HPLC (−1.5%).

In conclusion, disulfiram *in substantia* is characterised by relatively high radiochemical stability and could be sterilised by irradiation if not for the change in colour produced by the appearance of free radicals. The changed colour disappears in 16 months, but it is too expensive to store the substance for such a long time after sterilisation. In view of the above results, disulfiram is likely to be sterilised by methods other than irradiation.



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