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THERMAL STABILITY OF γ-IRRADIATED TOLBUTAMIDE

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Abstract

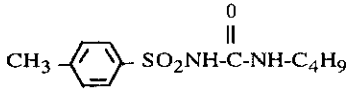
The thermal stability of tolbutamide before and after exposure to various γ-radiation doses was investigated. The data were followed by studying DTA, X-ray diffraction, IR, and UV absorption spectra before and after γ-irradiation. The results obtained were promising, and were explained, and discussed on the basis of γ-enhanced stabilization through recombination of free radicals.

Keywords: DTA, γ-radiation doses, IR, thermal stability, tolbutamide, UV

Introduction

Tolbutamide is 1-butyl-3-tosylurea [1], sulfonamide but not a sulfanilamide derivative.

Tolbutamide is a sulfonylurea drug in current use. It is an orally active hypoglycemic agent which reduces the blood sugar concentration. It probably acts by



stimulating insulin secretion, as it has no action on muscle-glucose metabolism when given alone [2].

The investigation of radiation damage in various materials has begun relatively recently; however, in the last few years, considerable progress has been made in this area. Radiation effects in solids are of great importance and are sometimes also an emotional issue [3–6].

The γ-ray spectrum of a radionuclide is a valuable tool for the qualitative identification of γ-ray emitting radionuclides. The full energy peak, or the photopeak, is identified as the γ-ray transition energy that is given in the decay scheme of the radionuclei.

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In irradiation with ^{60}Co gamma rays, the Compton effect has the larges cross-section [7] except for materials of very high atomic number and, moreover, the number of atoms displaced (cm^{-3} S^{-1}) is maximum in the very light elements and diminishes [8] to zero around atomic masses of 125. Irradiation with these rays therefore involves atomic displacement by the Compton electrons. Photoelectric and pair production events appear.

An electron spin resonance study of radiosterilization of antibiotics has been carried out by measurement of γ-ray-irradiated ceftazidime and ampicillin [9, 10]. Several studies have been carried out on the applicability of thermal analysis to investigate drugs [11].

The present work was carried out in view of assessment of the effect of γ-radiation on the physicochemical properties and thermal stability of tolbutamide. This effect was examined by recording the DTA curve before and after each γ-dose supplemented by X-ray diffraction, IR, and UV absorption studies. While significant work has been done on the effect of irradiation on the thermal decomposition of simple inorganic compounds, the effect exerted on pharmaceuticals is still not clear.

Through studying γ-induced changes in thermal behaviour, the determination of some constants and characteristics by thermal analysis is also aimed at.

Experimental

Tolbutamide is a pure substance and satisfies British Pharmacopeia (B.P.) requirements. All chemicals used were of analytical grade.

The X-ray diffraction patterns were recorded with a Shimadzu-XI-3 diffractometer using a CuK_α radiation and Ni filter. DTA measurements were made with an XD-30 thermal analyzer in air up to 500°C. The IR absorption spectra were recorded for KBr pellets with a Shimadzu (Japan) spectrophotometer in the range (4000–200 cm^{-1}). A Beckman DU-8-spectrophotometer was used for the UV absorption measurements in the range (200–350 nm) in ethanolic solution.

A group of samples of tolbutamide (four samples) were irradiated with different doses ranging from 0.192 KGy up to 8.830 KGy from a Cs-137 source as in Table 1. The Cs-137 source was calibrated with a dosimeter 2507 under its optimum conditions. The dose rate was 0.2666 Gy/min at 0.3 m from the source in air.

Table 1 γ-doses given to the examined compound

Dose/No	Dose (KGy)
I_o	0.000
I_a	0.192
I_b	2.087
I_c	5.374
I_d	8.83

Results and discussion

Results of X-ray diffraction studies

On examining the X-ray diffraction patterns before and after irradiation, Fig. 1, the following mechanism is suggested:

$I_o + 1^{st}$ dose I_a → decomposition

$I_a + 2^{nd}$ dose I_b → further decomposition

$I_b + 3^{rd}$ dose I_c → γ-enhanced melting resulted in a decreased degree of crystallinity as reflected by the broadening and weakening of X-ray diffraction peaks.

$I_c + 4^{th}$ dose I_d → γ-enhanced recombination of the formed free radicals to give I_d X-ray pattern.

But the I_d pattern is characterized by peak weakening and broadening due to the heating effect and softening by a strong γ-radiation dose (8.83 KGy).

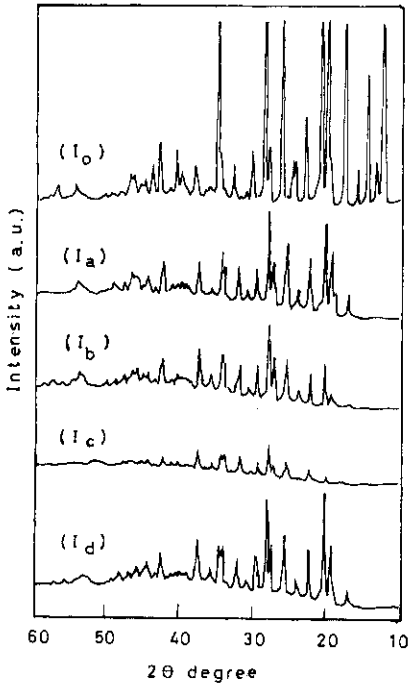

Fig. 1 X-ray diffraction pattern of tolbutamide before and after γ-irradiation

Differential thermal analysis (DTA)

Figure 2 displays the DTA curves for tolbutamide taken before and after each γ-absorbed dose. From the curves an identical trend is traced as that deduced from the present X-ray data as a function of the γ-radiation dose (Table 2, and Fig. 2).

Table 2 DTA reactions of tolbutamide before and after irradiation

No	Endothermic peak/ °C	Exothermic peak/ °C
I_o	128–260–330–360	490
I_a	130–270–320–350	–
I_b	130–260–310–350	475
I_c	130–260–296–320	420
I_d	130–260–310–350	430

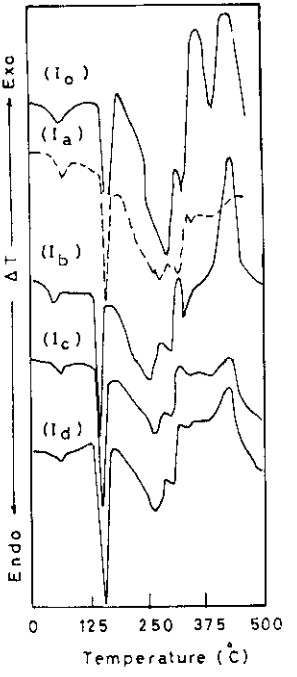

Fig. 2 DTA curves of tolbutamide before and after γ-irradiation

As shown in Fig. 2, the DTA curves of tolbutamide before and after γ-radiation doses display the following features:

1) The DTA curves of tolbutamide before γ-irradiation show an endothermic peak at 128°C corresponding to the melting of tolbutamide, followed by another endotherm at 255°C, due to lattice rearrangement for polymorphic transformation. There are also two exothermic peaks at 390 and 490°C, due to an oxidative thermal decomposition of the material which occurs in two steps at 390 and 420°C.

2) On examining the DTA curves of the γ-irradiated samples, the following conclusions can be drawn:

a) The DTA curve of sample I_a shows the disappearance of the decomposition peaks at 390 and 490°C, which is explained by a thermal stabilization induced by γ-radiation. The decomposition peaks were shifted to higher temperatures indicating further γ-irradiation-induced thermal stabilization.

b) The second decomposition peak decreased in intensity after the third dose I_c and again appeared at 420°C.

c) After the fourth γ-radiation dose, the second decomposition peak appearing at 420°C grows.

This is explained by assuming that, as a result of the absorbed γ-dose, the material undergoes thermal stabilization which increases further with increasing γ-radiation dose energy. This is in accord with all the results obtained in the present work for the first time.

Table 3 collects the activation energies of thermal decomposition using Piloyan's method [12]. The data in Table 3 show the general trend that E_a increases with increasing γ-dose up to 8.83 KGy.

Table 3 Activation energy (E_a) calculated from DTA data

Material No	E_a/ kJ mol^{-1}
I_o	30.79
I_b	168.0
I_c	193.2
I_d	22.39

Table 4 shows the reaction orders calculated from DTA curves taken before and after each γ-radiation dose. The following observations can be made:

a) For a non-irradiated sample the reaction order is near unity, indicating its clear first order type.

b) For a γ-irradiated sample, the reaction order exceeds unity by fractions depending on the γ-radiation dose. This indicates a composite reaction due to γ-radiation damage which may induce other reactions beside the first order ones.

Table 4 Reaction order calculated from DTA data before and after each γ–radiation doses

Material No	γ-rad. dose (KGy)	Reaction order (n)
I_o	0.00	1
I_a	0.1921	–
I_b	2.687	0.93
I_c	5.374	1.10
I_d	8.83	0.92

Results of IR studies

Figure 3 and Table 5, display the IR spectra of tolbutamide before and after γ-irradiation. The IR peaks of tolbutamide before irradiation were assigned as follows: 3320, 3190 cm^{-1} (urea, NH stretch) 2920, 2850 cm^{-1} (alkane, CH stretch) 1700, 1600 cm^{-1} (urea, C=O stretch), 1600, 1500 cm^{-1} (aromatic C=C stretch), 1555 (urea, amide II), 1640, 1375 cm^{-1} (alkane, CH deformation) 1335, 1160 cm^{-1} (sulfonamide, S=O stretch). The structure is supposed to be stabilized by hydrogen bonding between the polar group and van der Waals interactions between the non polar groups. Thus, a hydrogen-bond network and the dynamics of

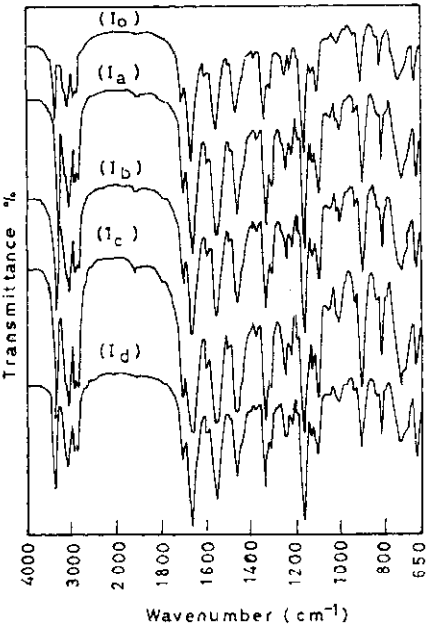

Fig. 3 IR spectra of tolbutamide before and after γ-irradiation

Table 5 Characteristic IR absorption spectra of tolbutamide at various doses and their band assigments

1st dose (0.0 KGy)	2nd dose (0.1921 KGy)	3rd dose (2.687 KGy)	4th dose (5.374 KGy)	5th dose (8.83 KGy)	Assignment
3350	3350	3350	3350	3350	Urea–stretch
3100	3100	3100	3100	3100	NH–stretch
2900	2900	2900	2900	2900	Alkane–stretch
–	1920	1920	1920	1920	New band
1700	1700	1700	1700	1700	Urea–stretch
1670	1670	1670	1670	1670	C=O–stretch
1555	1555	1555	1555	1555	Urea–amide II
1335	1335	1335	1335	1335	Sulfonamide
1160	1160	1160	1160	1160	S=O Stretch

the protons are of great importance in explaining the properties of the crystals and their phase transitions.

After γ-dose absorption, as supported by X-ray data, the IR absorption spectra exhibit the following changes:

1 – peak broadening,
2 – increased intensity up to the third dose,
3 – appearance of new bands (e.g. at 1920 cm^{-1}),
4 – change in relative intensity.

All of these could be ascribed to the damage due to γ-irradiation causing a reduced degree of crystallinity (Fig. 3 and Table 5).

Electronic absorption spectra

The effect of γ-radiation doses on the electronic absorption spectra of tolbutamide was studied by using 20 $\mu g \cdot mL^{-1}$ in anhydrous ethanol in the range 200–350 nm.

Comparison of the electronic absorption spectra of tolbutamide Fig. 4 before and after γ-irradiation reveals that:

1) The absorption spectrum of tolbutamide before irradiation shows λ_{max} at 228 nm. The same result was obtained after the 1st γ-radiation dose.

2) The absorption spectra of tolbutamide after the 2nd, 3rd and 4th radiation doses display a new band at 270 nm and the absorbance changes as in Fig. 5. This can be due to γ-pyrolysis as a result of γ-radiation damage leading to some polymorphic transformation.

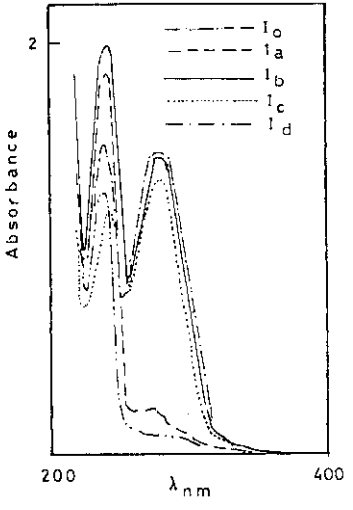

Fig. 4 Effect of γ-irradiation on the electronic absorption spectra of tolbutamide

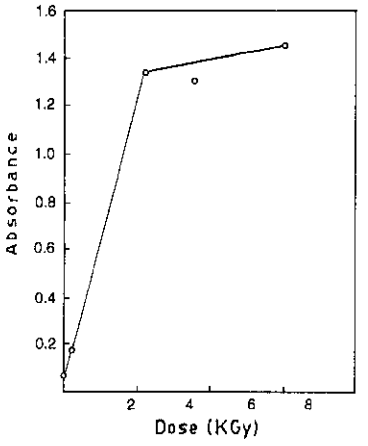

Fig. 5 Relation between absorbance and dose of γ-radiation

Table 6 displays the variation of absorbance with absorbed γ-dose from which it can be concluded clearly that tolbutamide can be used successfully as a γ-dosimeter up to 2.687 KGy.

Table 6 Variation of absorbance with absorbed γ-dose at λ =270 nm

Dose	Absorbance
I_o	0.072
I_a	0.19
I_b	1.21
I_c	1.12
I_d	1.22

Conclusions

The DTA, X-ray diffraction, IR, and UV absorption spectra, permitted studies on the thermal stability of γ-irradiated tolbutamide.

* * *

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