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γ-INDUCED THERMAL STABILITY AND THERMAL STUDIES ON TIMOLOL β-BLOCKER

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Abstract

Timolol drug, has been investigated by using X-ray diffraction analysis, thermogravimetry (TG), differential thermal analysis (DTA), IR, HPLC and electronic absorption spectra (UV/Vis), before and after exposure to γ-radiation. The interaction of γ-rays with timolol has been studied. Results obtained indicated high stability toward γ-absorbed dose over the range 5–50 kGy.

Keywords: β-blocker, HPLC, IR, γ-radiolysis, thermal stability, timolol, UV, X-ray

Introduction

Timolol is (-)-1-(tert-butylamino)-3-{(4-morpholino-1,2,5-thiadiazl-3-yl)oxyl}-2-propanol. It is a β adrenergic blocker which is widely used in patients with open-angle glaucoma and a phakic glaucomais also medicated for the treatment of hypertension and available for oral dosing as tablets and for injection and ophthalmic dosing as distinct sterile aqueous solution [1]. Reformulation compatibility studies between timolol maleate and tablet excipients using differential scanning calorimetry (DSC) [2] was carried out. The centres of decomposed materials grow up and ultimately fracture the crystal [3].

Radiation effects on solids are subjects of great importance to investigate one or more feature of the decomposition process [4–7]. Many recent studies on the decomposition of solids have included measurements on samples irradiatied prior to heating. These measurements were performed for one or both of the following reasons. Firstly, the material may have been irradiated to investigate one or more feature of the decomposition process. Secondly, it may have included in a 'radiation damage' study to determine if radiation can modify one or more properties of the material in an im-

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portant way by creating point defects or increasing the number of nucleation forming sites [8]. ESR study of radio sterilization of antibiotics was applied to the study of γ-rays irradiated cefazidine, and ampicillin and cefoperzone [9–11] . The effect of γ-irradiation on the degradation of salbutamol was evaluated [12] process control, and dosimetry in multipurpose irradiation facility were carried out [13]. The thermal stability of γ-irradiation of tolbutamide was studied [14].

In continuation to our previous work [14, 15] the present investigation was carried out in view of assessment of the effect of γ-radiation on the thermal stability of timolol. This effect was examined by recording TG, DTA curves before and after γ-irradiation and supplemented by XRD, IR, UV and HPLC studies. The major goal of the present manuscript is to promote thermal stability and hence to lengthen the expiry time by γ-irradiations and to throw light on its γ-pyrolysis.

Experimental

Timolol maleate is a pure substance satisfying US pharmacoepia requirements. All chemicals used are BDH of pure analytical grade 99.5%.

Equipment

X-ray diffraction patterns were recorded with Philips analytical X-ray BV. Diffractometer type PW 1710 Based using anode CuK_{α} tube (UK). TG and DTA measurements were carried out using a Shimadzu DT 30 thermal analyzer with platinum crucible and a heating rate of 10°C min^{-1} up to 500°C. IR absorption spectra were recorded using KBr pellet on a Shimadzu spectrometer in the range (200–4000 cm^{-1}). HPLC system consisted of a pump (Perkin Elmer) series 200 Ic A with a UV visible detector (Perkin Elmer 785 A), a data computer system was used. Separation was carried out on a Bondapak C18 (10 μm, 300 3.9 mm id). The mobile phase consisted of methanol/acetonitrile/phosphate buffer (10 mM) (15:15:70 *v/v/v,* pH 3). Flow rate was 1 mL min^{-1} at ambient temperature. UV measurments were undertaken at 254 nm.

Electronic absorption spectral measurements were carried out using Perkin Elmer Lambda 20/1.0 nm/vis. Spectrometer (1.01) 22A (scan method) wave minimum (200 nm) and wave maximum (400 nm).

γ-Irradiation was carried out in order to determine the effective dose for sterilization. Cs-137 γ-radiator (activity source 500 Ci) at a dose rate 0.4 cGy s^{-1} at distance 30 cm from the source was used, at the National Institute of Standard, Giza, Egypt.

The various solid samples (timolol) were exposed to various γ-absorbed doses from 5 up to 60 kGy in air.

Results and discussion

X-ray diffraction before and after γ-irradiation

Figure 1 displays the X-ray diffraction patterns of timolol β-blocker before γ-irradiation.

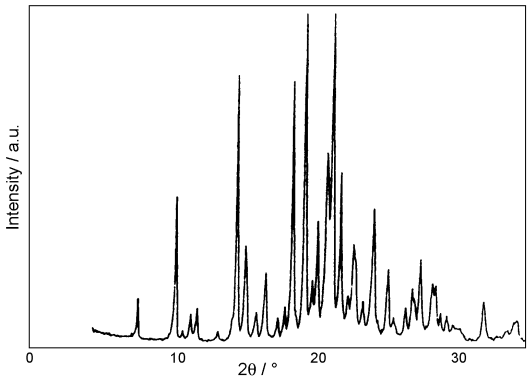

Fig. 1 X-ray diffraction patterns of timolol β-blocker before γ-irradiation

It can be seen from Fig. 1 that the X-ray diffraction patterns belong to the pure structure of timolol. This agrees with previous results [16]. As a result of absorption of 5 kGy γ-irradiation, the relative intensity (counts) of the diffraction peaks suffer a decrease in intensity without a phase change. Thus, the material identity is still preserved. The observed decrease in relative intensity is due to partial dissociation of the material induced by γ-absorbed dose [14]. The relative intensity rises again reaching a maximum after 15 up to 50 kGy γ-irradiation with still preservation of material identity. This increased intensity explains the increased material degree of crystallinity. Above this dose, (>50 kGy) the material undergoes partial dissociation. This criteria is explained in details regarding Fig. 2 for the variation of relative peak intensity with γ-irradiation of timolol β-blocker on examining the X-ray diffraction patterns before and after irradiation, suggested the following scheme for γ-irradiation of timolol (Ti):

$\xrightarrow{\text{Ti+1st dose 5 kGy}}$ Dissociation, γ-enhanced melting resulted in a decreased degree of crystallinity as reflected from the weakening of X-ray diffraction peak intensity.

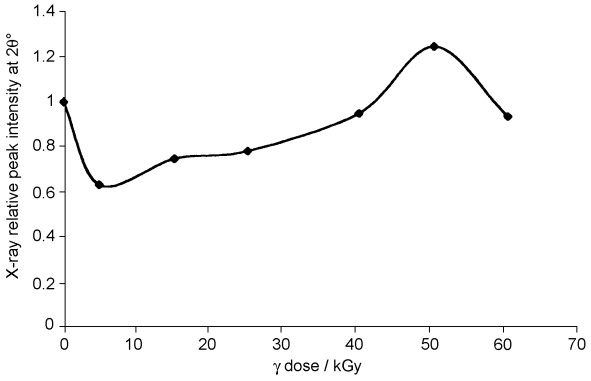

Fig. 2 The variation of relative peak intensity of X-ray *vs*. γ-absorbed dose for timolol β-blocker

$\xrightarrow{\text{Ti+ 2nd dose}\quad\text{15 kGy}}$ γ-Promoted enhanced the degree of crystallinity to give X-ray pattern [14, 15].

$\xrightarrow{\text{Ti+ 3rd dose}\quad\text{25 kGy}}$ Further γ-enhanced the degree of crystallinity to give X-ray pattern of the more crystalline material.

$\xrightarrow{\text{Ti+ 4th dose}\quad\text{40 kGy}}$ Further γ-enhanced the degree of crystallinity giving rise to an extremely crystalline product [14, 15].

$\xrightarrow{\text{Ti+ 5th dose}\quad\text{50 kGy}}$ Maximum degree of crystallinity is attained.

$\xrightarrow{\text{Ti+ 6th dose}\quad\text{60 kGy}}$ The material suffers induced decomposition due to γ-irradiation damage. Thus, the crystallinity decreases back again.

Thermal stability (TG, DTA)

Table 1 and Fig. 3 show collection of TG and DTA analyses of timolol as a function of γ-absorbed dose. Table 1 shows that some thermal parameters as melting point temperature, percentage of mass loss and heat enthlapy ΔH for timolol at different γ doses were measured. Figure 3a shows that thermal behaviour belongs to the pure structure of timolol before irradition [16]. After irradiaion Fig. 3b–d it can be easily seen that the behaviour of various γ-irradiation samples are identical to that of the unirradiated one. This indicates that, the thermal behaviour still preserves its identity, and γ-irradiation stabilizes it with the same slight change into the shape of endothermic and exothermic due to the same kind of lattice rearrangement as induced by both γ-irradiation damage and thermal effects as supported by X-ray data. These are ex-

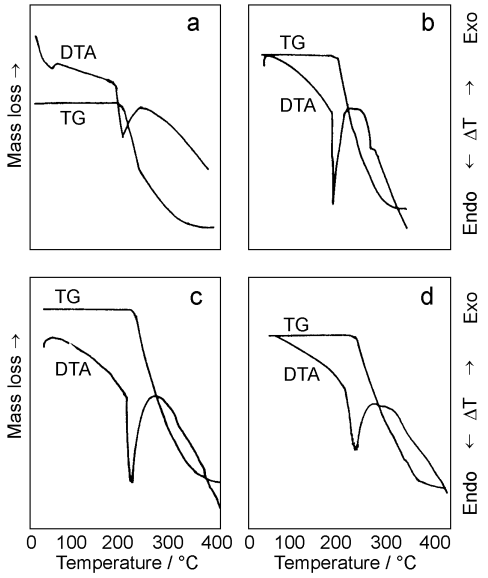

Fig. 3 The variation of thermogravimetric analysis (TG) and differential thermal analysis (DTA) of timolol as a function of γ-absorbed dose: a – before γ-irradiation; b – after γ-absorbed (5 kGy) dose; c – after γ-absorbed (25 kGy) dose; d – after γ-absorbed (50 kGy) dose

plained on the basis that, as the γ-irradiation doses energy increases from 15 up to 50 kGy the material undergoes thermal stabilization. This is in conformity with the results obtained by X-ray diffraction.

Table 1 Thermal behaviour (TG, DTA) and their assignment for timolol before and after γ-irradiation

Material	TG data		DTA-data		
	Temp. range/°C	Mass loss/%	Assignment	Temp. range/°C	ΔH/kJ g^{-1}
Before γ-irradiation	214		Endothermic peak due to melting	180–230	–0.40
	218–400	85	Dissociation of oxidation product		
After γ-absorbed 5 kGy	208		Endothermic peak due to melting	129–296	–0.45
	199–400	78.8	Dissociation of oxidation product		
After γ-absorbed 15 kGy	211		Endothermic peak due to melting	129–296	–0.60
	225–397	81.1	Dissociation of oxidation product		
After γ-absorbed 25 kGy	210		Endothermic peak due to melting	197–199	–0.51
	186–396	81.1	Dissociation of oxidation product		
After γ-absorbed 40 kGy	210.5		Endothermic peak due to melting	193.9–200	–0.32
	218–398	81.7	Dissociation of oxidation product		
After γ-absorbed 50 kGy	212		Endothermic peak due to melting	197–205	–0.55
	220–398	81.3	Dissociation of oxidation product		

Results and discussion of IR studies

The characteristic IR absorption spectra of timolol before and after γ-absorbed doses from 5 up to 60 kGy revealed revaled that the absorption bands for OH, NH, C=N, C–O, C–OH and C–O–C are not affected by irradiation over the rang 5–50 kGy.

High-performance liquid chromatography (HPLC) results and discussion

Figure 4 represents the relationship between intensity of HPLC (peak area) and γ-irradiation of timolol. It can esily be seen that the separation of timolol active ingredi-

ent before irradiation took place at a retention time (2.45 min) and peak area (121 μv s), (Fig. 4a). After the first radiation dose (5 kGy) the peak area decreased to (99 μv s), (Fig. 4b); i.e. the value of the peak area is lower than the unirradiated timolol active ingredient by 18%.

After γ-irradiation doses (15–50 kGy) (Fig. 4c–f) the peak area increased again to return to the initial value (unirradiated). This explains that there is a good degree of crystallinity of timolol with the increase of γ-doses up to (50 kGy) via plymerization and /or recombination.

Electronic absorption spectra

Figure 5 represents the relation between electronic absorption (UV) and γ-irradiation for timolol before and after γ-irradiation's .The spectra in all cases are similar (294 nm) indicating that the material still preserves its identity after γ-irradiation. The variation of optical density of the spectra with γ-absorbed dose displays the same trend exactly as depicted from our preceding X-ray and (HPLC) data.

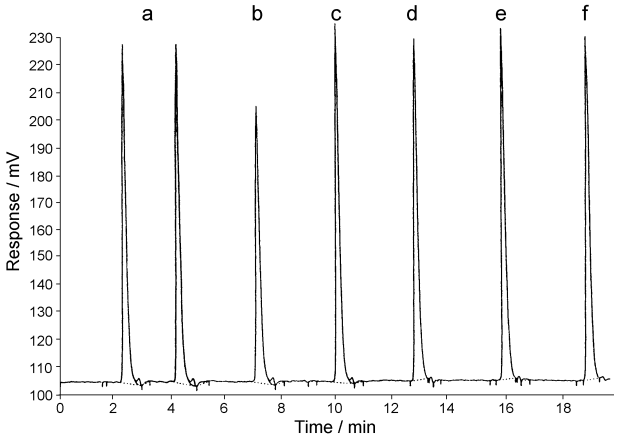

Fig. 4 Relationship between intenisity of HPLC (peak area) of timolol and γ-irradiation before (a) and after (b–f) γ-absorbed doses

According to the results of X-ray diffraction, UV absorption and HPLC, one can expect that when the drug is exposed to (5 kGy) there is a dissociation in the active ingredient which leads to reduction in the expiry date. But exposure to (15–50 kGy) can lead to a good degree of crystallinity due to recombination, which may lengthen the expiry date. This explains and proves the full agreement amongst the three tools of research X-ray, HPLC and UV/Vis as mentioned above for the scheme of interaction of γ-irradiation with timolol and stability of timolol towards γ-absorbed doses in the range investigated.

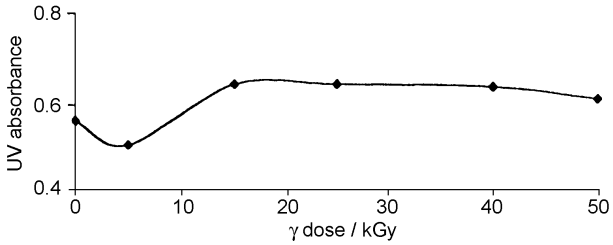

Fig. 5 Relation between electronic absorbance (UV) and γ-absorbed dose of timolol β-blocker after and before irradiation's

Conclusions

Timolol β-blocker displays high resistance to nuclear γ-irradiation above 5 to 50 kGy throughout a γ-induced, as detected from the increasing of the X-ray peak intensity and hence its degree of crystallinity. Results and discussion given for X-ray analysis, high performance liquid chromatography (HPLC) and electronic absorption spectra (UV/Vis) are in conformity. Accordingly, γ-irradiation doses above 5 to 50 kGy could be used safely for sterilization of timolol β-blocker for special applications.

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