Physico-Chemical and Analytical Study of Metoprolol Tartrate: An Antihypertensive Drug

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Metoprolol active ingredient has been investigated using X-ray diffraction analysis, thermogravimetry, differential thermal analysis, infrared and high-pressure liquid chromatography before and after exposure to 5 up to 50 kGy absorbed dose. The results obtained indicated high stability of metoprolol toward γ -absorbed dose. The scheme of interaction of γ -rays with metoprolol has been considered.

Keywords: X-ray, IR, UV, HPLC, γ -Radiolysis, Thermal stability, Metoprolol.

INTRODUCTION

Metoprolol tartrate is a synthetic selective β -1 adrenoceptor-blocking agent. Chemically, metoprolol is 1-[4-(2-methoxyethyl)-phenoxy]-3-[(1-methylethyl)amino]-2-propanol (2:1) dextro-tartrate salt (**Scheme-I**). Clinical trials demonstrate that most the hypertensive patients will not achieve goal blood pressure with a single drug alone, further supporting the use of multi drug therapy [1]. Combining drugs with complementary mechanisms of action permits use of lower doses of each, reducing the risk of dose-dependent adverse reactions. Combinations of β -blockers and diuretics, usually hydro thiazide class are very common in antihypertensive therapy [2]. Combination is official in the United States Pharmacopoeia which recommended liquid chromatographic assay with two different chromatographic conditions for each of drugs [3]. Various methods have been reported in the literature for simultaneous determination of metoprolol and hydrochlorothiazide in tablet dosage forms which includes spectrophotometry [4-9], high performance liquid chromatography [8-15] and electrophoresis [16].

Scheme-I

The radiostability of aqueous solutions of metoprolol tartrate and the influence of absorbed dose (0-50 kGy), dose rate (e-beam vs. gamma) and radioprotectors (pharmaceutical excipients) are investigated by HPLC-UV analyses and through computer simulations [17]. In continuation to our previous work on the γ -irradiated drug [18] the present manuscript is to enhance promote thermal to throw a light on the γ -pyrolysis. In drug industry, companies pay attention to sterilization. These investigated revealed the possibility to use γ -irradiation to sterilize metoprolol with safety dose.

EXPERIMENTAL

Metoprolol tartrate is a pure substance and satisfies US-pharmacopeia requirements. All chemicals used are of analytical grade (purity 99.5 %).

Irradiation facility: A group of samples of metoprolol, were irradiated with different absorbed dose ranging from 5 kGy up to 50 kGy using a Cs-137 source. The absorbed dose rate, 0.4 cGy was measured using Famer dosimeter (S.No. NE 2571) under the optimum conditions of γ -irradiation, at 30 cm from the source in air, at (National Institute for Standard), Egypt.

X-ray diffraction patterns were recorded with Philips analytical X-ray BV. Diffractometer type pw1710 BASED using anode Cu-K α tube.

TGA and DTA measurements are carried out using SHIMADZU DT 30 thermal analyzer with platinum crucible. Two different temperature programs were designed for metoprolol before and after γ -irradiation. First, different sample

masses of metoprolol were used at a heating rate of 10 °C/min from 25-500 °C. The second, fixed sample masses of metoprolol were used in an oven temperature at a heating rate 10 °C/min from 25-500 °C.

IR spectra were recorded KBr pellet with a SHIMADZU (Japan). Metoprolol is mixed with dry KBr in a ratio 1:100 before and after absorbed dose.

The HPLC separations consisted of a pump (Perkin-Elmer) series 200lc with an UV visible detector and a data computer system. Separation was carried out on a chromegaband M C18 (250 cm. 10 µmm, 4.6 mm id) column. The mobile phase consisted of 50 mM Na₂HPO₄ acetonitrile (7:3), pH 3.5. Flow rate was 1 mL/min at room temperature, UV measurements was at 220 nm and manual injection for all samples.

All the samples were prepared with fixed concentration (0.0001 M) from metoprolol before and after absorbed dose, then 50 µL for sample were injected in HPLC equipment.

RESULTS AND DISCUSSION

X-ray studies: Fig. 1 and Table-1 display the X-ray diffraction patterns of metoprolol tartrate β-blocker (Fig. 1a) and after (1b-f) γ-absorbed doses. It can be seen from (Fig. 1a) that the X-ray diffraction patterns belong to the pure structure of metoprolol, agree with the previous result [19]. As a result of absorption of (5-15) kGy absorbed dose, the relative peaks intensity (counts) of diffraction peaks suffer a decrease in relative intensity without phase change (Fig. 1b-c).

Thus, the material identity is still preserved and the observed decrease in relative intensity is due to partial dissociation of material induced by absorbed dose [18]. The relative intensity rises again reaching a maximum after 20 up to 40 kGy absorbed dose with still preservation of material identity. This increased intensity explains the increased material degree of crystallinity (Fig. 1d-e). Above this dose, (40 kGy) the material undergoes back partial dissociation. This criterion is explained in details regarding (Fig. 2) for the variation of relative peak intensity with γ-irradiation of metoprolol.

It can be seen from these Figs. 1 and 2, the X-ray diffraction patterns belong to the pure structure of metoprolol tartrate [19-21]. Thus the material identities are still preserved. The observed decrease in relative intensity is due to partial dissociation of the materials induced by γ-irradiation [22]. This increased intensity due to the increased material degree of crystallinity, as caused by induced free radical recombination, or through polymerization mechanism of some lattice structure.

On examining the X-ray diffraction patterns before and after γ-irradiation, we can suggest the **Scheme-II**, of the effect of irradiation on metoprolol (Mt).

Thermal studies (TGA, DTA): Figs. 3 and Table-2 show a collection of thermal analysis (TGA) and (DTA) of metoprolol tartrate before (a) and after (b-f) absorbed dose. Table-2 shows that some thermal promoters as melting point temperature, percentage of weight loss and heat enthalpy (ΔH) for metoprolol at different doses were measured. Fig. 3a shows

Fig. 1. X-ray diffraction patterns of metoprolol, β-blocker: (a) before irradiation; (b) after γ-absorbed (5 kGy) dose; (c) after γ-absorbed (15 kGy) dose; (d) after γ-absorbed (20 kGy) dose; (e) after γ-absorbed (40 kGy) dose; (f) after γ-absorbed (50 kGy) dose

TABLE-1
X-RAY DIFFRACTION ANALYSIS OF METOPROLOL TARTRATE BEFORE γ -IRRADIATION AND AFTER γ -IRRADIATION DOSES

2 θ (°)	Before γ -irradiation		After γ -irradiation									
	0 kGy		5 kGy		15 kGy		20 kGy		40 kGy		50 kGy	
	d (Å)	Counts	d (Å)	Counts	d (Å)	Counts	d (Å)	Counts	d (Å)	Counts	d (Å)	Counts
10.65	8.2961	2275	8.2845	511	8.3000	620	8.3351	1747	8.2459	2323	8.2961	2043
12	7.3691	1325	7.3752	331	7.3599	342	7.3967	1005	7.3235	1282	7.3820	1225
4.3	6.1865	1176	6.1624	299	6.1822	346	6.2016	829	6.1480	1005	6.1757	1024
15	5.8916	841	5.8857	216	5.9014	207	5.9131	615	5.8644	801	5.1757	824
15.9	5.3675	2767	5.5641	245	5.5710	754	5.5867	2016	5.5433	2642	5.8955	2642
16.9	5.2334	702	5.2144	180	5.2235	213	5.2435	538	5.2052	671	5.2220	692
18.17	4.8783	2927	4.8876	858	4.8796	876	4.8957	2430	4.8663	3102	4.8796	3003
17.4	4.5612	5388	4.5427	2134	4.5670	1806	4.5589	5069	4.5358	6304	4.5554	5432
20.5	4.3078	3564	4.3132	1444	4.3267	1459	4.3278	3329	4.3059	4007	4.3278	3564
21.62	4.104	1747	4.1117	552	4.1136	571	4.1230	1354	4.1014	1875	4.1089	1681
22.3	3.9701	635	3.9649	207	3.9614	207	3.9859	524	3.9684	756	3.9710	615
23.19	3.8324	3192	3.8340	1024	3.8324	1116	3.8406	2470	3.8218	3306	3.8332	2970
23.64	3.7604	1552	3.7612	605	3.7597	645	3.7707	1421	3.7518	1892	3.7628	1648
24.0	3.6942	2905	3.7010	1096	3.6980	1183	3.7087	2746	3.6906	3411	3.6973	2992
25.31	3.5247	7.8	3.5173	262	3.5139	282	3.5221	676	3.5024	801	3.5126	704
26.2	3.3909	467	3.3928	172	3.3947	202	3.4030	408	3.3896	529	3.3966	462
26.79	3.333	286	3.3226	100	3.3226	104	3.3281	279	3.3207	372	3.3348	313
27.53	3.2453	404	3.2370	139	—	—	3.2460	416	3.2402	571	3.2512	462
28.01	3.1813	317	3.1796	117	3.1597	114	3.1674	256	3.1751	467	3.1690	384
29.4	3.0294	586	3.0451	202	3.0360	216	3.0497	581	3.0355	812	3.0350	586
31.65	2.8317	296	2.8307	114	2.8277	123	2.8351	310	2.8281	437	2.8273	369
33.1	2.7026	428	2.6911	174	2.935	177	2.6947	445	2.6947	586	2.6884	420
34.4	2.6005	376	0	0	0	0	2.5946	412	2.5852	600	2.5849	454

Fig. 2. Variation of relative peak intensity of X-ray versus γ -absorbed dose for metoprolol

that thermal behaviour belongs to the pure structure of metoprolol. After irradiation (Fig. 2b-f), it can be easily seen that the behaviour of various γ -irradiation samples are identical to that of unirradiated one. This indicates that the thermal behaviour still preserve its identity and γ -irradiation stabilizes it with the same slight change into the shape of endothermic and exothermic due to some kind of lattice rearrangement as induced by both absorbed dose damage and thermal effects as supported by X-ray data.

(Mt) + zero dose:

(Mt) + 1st dose 5 kGy:

(Mt) + 2nd dose 15 kGy:

(Mt) + 3rd dose 20 kGy:

(Mt) + 4th dose 40 kGy:

(Mt) + 5th dose 50 kGy:

X-ray diffraction patterns belong to the pure structure of metoprolol [Ref. 20] (Fig. 1a)

Dissociation, γ -enhanced melting resulted in a decreased degree of crystallinity as reflected from the weakening of X-ray diffraction peak intensity (Fig. 1b)

Further dissociation (Fig. 1c)

γ -enhanced recombination of the formed free radicals to give (Fig. 1d) X-ray pattern

Further γ -enhanced recombination of the formed free radicals to give X-ray pattern of more crystalline (Fig. 1e)

The material suffers induced decomposition due to γ -irradiation damage. Thus the crystallinity decreases back again (Fig. 1f)

IR studies: Fig. 4 and Table-3 displays the IR spectra of metoprolol tartrate before (a) and after (b-f) absorbed doses of 5 up to 50 kGy. The IR spectra of metoprolol tartrate before irradiation were assigned as flow 3600–2300 cm^{-1} (NH_2 , OH), 1580 cm^{-1} , carboxylic acid salt), 1100 cm^{-1} (aliphatic ether). IR spectra indicate that no change or disappearance in the position of the characteristic bands are observed. From this result, the IR absorption spectra suffer.

(i) Decreased intensity of peaks after dose 5 kGy.

(ii) Increased intensity of peaks after doses 40 kGy with β -blockers metoprolol without change or shift in the bands of IR spectra.

UV spectra: The effect of γ -irradiation doses on the electronic absorption spectra of β -blockers metoprolol was studied by using 20 mg mL^{-1} in anhydrous ethanol. Fig. 5 represent the relation between electronic absorption (UV) and γ -irradiation doses before and after γ -absorbed doses. The spectra in all cases at the same wavelength related to the each substance. This indicated that the materials still preserve its identity after γ -absorbed doses. The variation of optical density of the spectra with γ -absorbed doses displays the same trend

TABLE-2
THERMAL BEHAVIOUR (TGA, DTA) AND THEIR ASSIGNMENT FOR METOPROLOL BEFORE AND AFTER γ -IRRADIATION

Material	TGA data		DTA data		
	Temp. range ($^{\circ}\text{C}$)	Weight loss (%)	Assignment	Temp. range ($^{\circ}\text{C}$)	ΔH (kJ/g)
Before γ -irradiation	126.9		Endothermic peak due to melting	104.5-142.3	-34.6
				189.8-238.5	-32.8
	159.9-487	96.0	Exothermic peak due to step wise oxidative decomposition	244-287	116.9
				287-438.8	-19
After γ -absorbed 5 kGy	127.4		Endothermic peak due to melting	109-145	-141.9
			Exothermic peak due to stepwise oxidative decomposition	109-145	-141.9
	171.8-334	88.4	Endothermic peak due to dissociation of oxidative products	250-302.8	-80.35
After γ -absorbed 15 kGy	126		Endothermic peak due to melting	99.8-143.6	-102.7
			Exothermic peak due to stepwise oxidative decomposition	194.8-239.7	-81.8
	161-334.6	94.7	Endothermic peak due to dissociation of oxidative products	249.2-304	-83.7
After γ -absorbed 20 kGy	126.7		Endothermic peak due to melting	109.8-145.9	-132
			Exothermic peak due to stepwise oxidative decomposition	184-240	-144
	161-400	94.5	Endothermic peak due to dissociation of oxidative products	390-432	-281
After γ -absorbed 40 kGy	126.9		Endothermic peak due to melting	105-144	-108
			Exothermic peak due to stepwise oxidative decomposition	197.9-234	-130
	174-336.6	94.1	Endothermic peak due to dissociation of oxidative products	247-310	-130
After γ -absorbed 60 kGy	126.5		Endothermic peak due to melting	97.5-146.8	-119.3
			Exothermic peak due to stepwise oxidative decomposition	185-242	-115.7
	179-487	94.9	Endothermic peak due to dissociation of oxidative products	247.6-309	-120.4

Fig. 3. Variation of thermogravimetric (TGA) and differential thermal analysis (DTA) of metoprolol as a function of γ -absorbed: (a) before irradiation; (b) after γ -absorbed (5 kGy) dose; (c) after γ -absorbed (15 kGy) dose; (d) after γ -absorbed (20 kGy) dose; (e) after γ -absorbed (40 kGy) dose; (f) after γ -absorbed (50 kGy) dose

Fig. 4. IR absorption spectra of metoprolol at various γ -absorbed doses (a-f), (a) before irradiation; (b) after γ -absorbed (5 kGy) dose; (c) after γ -absorbed (15 kGy) dose; (d) after γ -absorbed (20 kGy) dose; (e) after γ -absorbed (40 kGy) dose; (f) after γ -absorbed (50 kGy) dose

Fig. 5. Relation between electron absorbance (UV) and γ -absorbed dose of metoprolol

exactly as depicted from our preceding X-ray and IR data. According to the results of X-ray diffraction, IR, spectra and UV absorption, we can expect that, when the drug (β -blockers), are exposed to 5 kGy, there are dissociation due to the effect of γ -irradiation, which leads to the decrease in peaks intensity. After the dose 20 kGy up to 50 kGy, the intensity increases due to recombination of free radical and good crystallinity induced by γ -irradiation.

HPLC: Fig. 6 represent the high pressure liquid chromatography chromatograms (HPLC) (peak area) and absorbed dose of metoprolol. It can easily be seen that the separation of metoprolol (with manual injection) active ingredient before γ -irradiation takes place at the same retention time (3.5 min) and peak area (602 μ V/s) (Fig. 6a). After the first absorbed

doses (5 up to 15 kGy) the peak area was decreased to (478 μ V/s) (Fig. 6b), *i.e.* the value of the peak area is lower than the unirradiated metoprolol active ingredient. These indicate that there is a partial dissociation of the active ingredient metoprolol as supported by X-ray. After absorbed dose (20-40 kGy) (Fig. 6c-d), the peak area explains that there is a good degree of crystallinity of metoprolol with the increase of absorbed dose up to (40 kGy).

Fig. 6. High performance liquid chromatography (HPLC) chromatogram of metoprolol before (a) and after (b-f) γ -irradiation

Conclusion

X-ray analysis, thermal analysis (TGA, DTA), IR spectra, UV analysis and high pressure liquid chromatography (HPLC) leads to good analysis that metoprolol β -blockers, high resistance to γ -absorbed doses from 20 up to 40 kGy throughout a γ -induced degree of crystallinity. Alternatively absorbed dose 20-40 kGy could be used safety for sterilization of metoprolol β -blockers for special application.

TABLE-3
KEY INFRARED ABSORPTION BANDS (cm^{-1}) AND THEIR BAND ASSIGNMENT OF
METOPROLOL β -BLOCKER AT 5 UP TO 60 kGy γ -ABSORBED DOSES

0.0 kGy dose	5 kGy dose	15 kGy dose	20 kGy dose	40 kGy dose	60 kGy dose	Assignment
3600-2300	3600-2300	3600-2300	3600-2300	3600-2300	3600-2300	$-\text{NH}_2$, OH, aliphatic and aromatic
1580	1580	1580	1580	1580	1580	Carboxylic acid salt
1580-1515	1580-1515	1580-1515	1580-1515	1580-1515	1580-1515	Aromatic ring
1250-1015	1250-1015	1250-1015	1250-1015	1250-1015	1250-1015	Aromatic ether
1180	1180	1180	1180	1180	1180	Isopropyl group
1100	1100	1100	1100	1100	1100	Aliphatic ether, secondary alcohol
820	820	820	820	820	820	1,4-Disubstituted benzene

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