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IR Laser-Induced Changes to L-adrenaline-D-hydrogentartrate Incorporated in KBr Matrices

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Changes in the pharmaceutical L-adrenaline-D-hydrogentartrate, incorporated in KBr matrices, induced by a pulsed carbon-dioxide Transversely Excited Atmospheric (TEA) laser, were observed. Modifications of the sample were monitored via infrared spectra. Special attention was devoted to the dependence of the sample changes on the laser energy density used. The irradiation of the pharmaceutical has been performed with two laser lines at wavelengths of about 10.6 μm. The laser lines coincide well with the absorption band of the pharmaceutical, which is assigned to the *ring* vibrations/*out-of-plane* OH deformation vibrations, within the carboxyl (COOH) group of L-adrenaline-D-hydrogentartrate. Laser energy densities of 1.20 and 1.70 J/cm^2 modified the pharmaceutical/compound. It was found that this modification is in essence a thermal effect. The level of change showed a dependence on the laser energy density, number of accumulated laser pulses and temporal shape of the pulse.

Key words: Laser modification; L-adrenaline-D-hydrogentartrate; Thermal decomposition; Carbon-dioxide TEA laser

INTRODUCTION

Investigations of interaction of electromagnetic radiation, including lasers, with organic compounds are of great fundamental and technological importance. Studies of this kind have become more frequent in the last two

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decades [1–3]. Laser radiation is superior to classical source of radiation with its monochromaticity, intensity, directionality, and coherency, and as such can be applied in pharmacy/chemistry [4–11]. The using of lasers in pharmacy/chemistry includes: structural characterization, impurity testing, surface quality inspection of drugs, monitoring pharmaceutical production processes, toxicological organic materials trace detection, applications in combinational chemistry, etc. Lasers can also be utilized for inducing and controlling chemical reactions, in analytical and preparative chemistry, etc.

Typically lasers used in pharmacy/chemistry operate in the infrared, visible, or ultra-violet region of the electromagnetic spectrum. The Nd:YAG, carbon-dioxide, and dye-laser systems are frequently employed for these applications.

Within the context of laser beam interactions with inorganic/organic compounds, particularly in the solid phase [12–14], the studies of laser interactions with pharmaceutical compounds are scarce in the literature.

The main purpose of this work was to study the effect of the interaction between carbon-dioxide TEA laser radiation and L-adrenaline-D-hydrogentartrate incorporated in KBr matrices. No data have been found in the literature on the influence of this type of laser, which emits infrared radiation at a wavelength of about 10 μm, on this type of pharmaceutical. Special attention was paid to monitoring infrared spectra of L-adrenaline-D-hydrogentartrate as a function of the laser energy density used.

The IR spectrum of L-adrenaline-D-hydrogentartrate sample, before and after laser irradiation, was observed in the spectral region from 2000 to 650 cm^{-1}.

L-adrenaline-D-hydrogentartrate has several synonyms as: adrenaline bitartrate, L-epinephrine-D-hydrogentartrate, etc. It is a L-3,4-dihydroxy-α-[(methylamino)methyl]-benzyl-alcohole-D-hydrogentartrate compound.

Generally speaking, adrenaline, as a specific hormone of the suprarenal medulla, acts as a chemical transmitter of the sympathetic nervous system [15]. The more general function is stimulating various metabolic processes under conditions of stress. It behaves as a reserve ready to be liberated in emergency conditions to support the actions of adrenergic nerves, which function by liberating chiefly noradrenaline. It is well known that adrenaline produces tachycardia and an increase in cardiac output.

As a drug adrenaline belongs to the sympathomimetic group of pharmaceuticals. It is rapidly taken up by the heart, spleen, several glandular tissues, and adrenergic nerves; only metabolites are detectable in the cerebrospinal fluid [16]. The major metabolic reactions are oxidative deamination and O-methylation followed by reduction or by glucoronic acid or sulphate conjugation.

EXPERIMENTAL

The solid L-adrenaline-D-hydrogentartrate used in the experiments was manufactured by Fluka Company. The level of sample purity was *biochemica*; >98%.

The samples were prepared in the form of standard pellets for infrared spectroscopy. Three milligrams of L-adrenaline-D-hydrogentartrate were mixed by grinding with 300 mg of KBr and pressed under evacuation in a standard die. The ratio between L-adrenaline-D-hydrogentartrate and KBr in the pellet was 1:100.

A Perkin Elmer grating infrared spectrophotometer Model 237, was used. The spectra were typically scanned from 2000 to 650 cm^{-1} spectral range at ambient temperature. All the spectra were recorded in the transmittance mode. During the recordings the pellet was covered by a mask with a central opening, 4 mm in diameter.

The pellet was irradiated by a pulsed TEA carbon dioxide laser [17] using a non-typical gas mixture of $CO_2/N_2/H_2$. The presence of nitrogen in the mixture resulted in longer laser-optical pulse, while hydrogen increased the efficiency of the laser system. Laser pulses typically included the initial spike, duration about 120 ns, and a tail with length of about 2 μs.

The laser beam had a spatial-uniform distribution of intensity. Detailed characteristics of the laser radiation are presented in Table I.

TABLE I The Typical Carbon-dioxide TEA Laser Operational Conditions During the Irradiation Experiments.

Gas mixture	$CO_2/N_2/H_2$
Content	1/1.6/1.4
Output pulse energy	⩽ 220 mJ
FWHM[a]	∼120 ns (initial spike); ∼2 μs tail.
Mode structure[b]	Multimode output
Beam divergence[c]	∼10 mrad
Laser cavity	nondispersive
Spectral composition[d]	Simultaneous two-line operation in the P-branch $00^{\circ}1 \rightarrow 10^{\circ}0$ vibrational band.
Pulse rate repetition	1 Hz

[a]Full width at half maximum. The laser pulse (temporal shape), for the $CO_2/N_2/H_2$ mixture, posses the initial spike, followed by a tail.

[b]The output of the laser is multimode. Unfocused laser beam has a cross section with dimensions of 1 cm × 1 cm.

[c]This value is measured in relation to the near field.

[d]The laser simultaneously operates at two wavelengths, *i.e.*, 10.5709 and 10.5909 μm, P(18) and P(20) transitions. The P(20) transition is more intense.

The pellet irradiation was performed with a slightly focused laser beam. The ZnSe lens with a focal length of 25.4 cm ensured delivering the laser beam onto the sample. The effective diameter at the target (pellet) was 4 mm and the angle of the laser beam with respect to the plane of the sample surface was 90°. The irradiation was conducted in air, at a pressure of 1013 mbar and relative humidity of 60%. During the experiment the pellet was not cooled. The samples were always irradiated with the same number of accumulated pulses, *i.e.* 4000 laser pulses.

RESULTS AND DISCUSSION

Infrared spectra of L-adrenaline-D-hydrogentartrate in KBr matrices recorded at room temperature (25 °C) before and after carbon-dioxide laser irradiation, are shown in Figures 1a and 1b, c, respectively. Thirteen absorption bands in the 2000 to 650 cm^{-1} spectral region, Figure 1a, were recorded before laser irradiation. Possible assignments of the bands are given in Table II. The tartrate group is linked to adrenaline probably via hydrogen bonds, Figure 2. Adrenaline is a secondary amine [15]; one atom of hydrogen in the group $-NH_2$ is substituted by CH_3. In the spectral region of 946 cm^{-1}, Figure 1a, L-adrenaline-D-hydrogentartrate has an absorption band of medium intensity. The measured FWHM of band was about 12 cm^{-1}. The frequency of this vibration band contributes to the *ring* vibrations of the aromatic group. *Out-of-plane* OH deformation vibrations of the carboxyl group within L-adrenaline-D-hydrogentartrate compound are in the same spectral region, Table II.

In the course of the experiment the L-adrenaline-D-hydrogentartrate was simultaneously irradiated with two laser lines at wavelengths of 10.5709 (945.993 cm^{-1}) and 10.5909 microns (944.2068 cm^{-1}), *i.e.* P(18) and P(20) lines, Figure 3. The P(20) line was more intense. Both laser lines strongly coincidence with the vibrational band at 946 cm^{-1}, *i.e.* with the *ring* vibrations/*out-of-plane* OH deformation vibrations (COOH group) inside L-adrenaline-D-hydrogentartrate. The effect of the carbon-dioxide laser radiation on the pharmaceutical is presented in the spectra Figures 1b and c, respectively. Generally speaking it was found that the changes were dependent on the laser energy density number of accumulated laser pulses, temporal shape of pulse, etc. It can be assumed that the energy absorbed, from laser beam by the sample, redistributes and facilitates breaking of some bonds, leading eventually to decomposition of the compound.

The laser energy densities used, 1.20 and 1.70 J/cm^2, have produced changes in the infrared spectra of pharmaceutical, Figures 1b and c. These

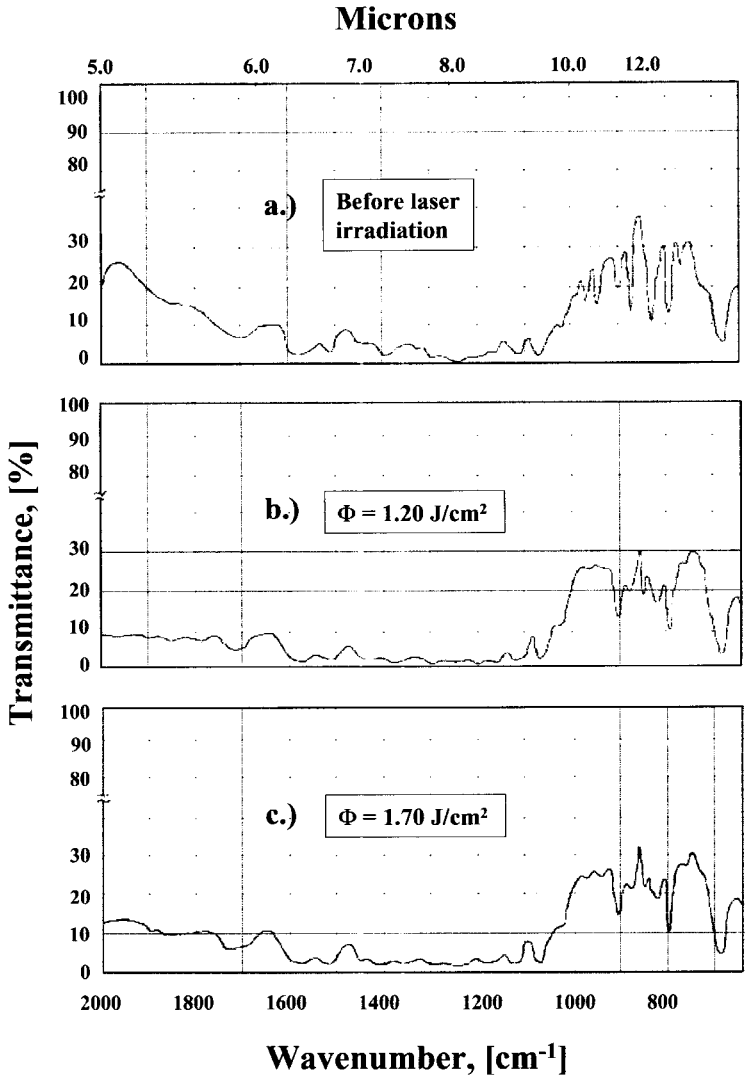

FIGURE 1 Infrared spectra of L-adrenaline-D-hydrogentartrate: (a) before, and (b), (c) after laser irradiation procedure. Spectra (b) and (c) are associated with accumulated action of 4000 laser pulses.
(Φ-laser energy density; L-adrenaline-D-hydrogentartrate: KBr = 1:100; $t = 25°C$).

TABLE II Infrared Absorption Bands of L-Adrenaline-D-Hydrogentartrate.

Frequency of the band [cm^{-1}]	*Suggested assignments*
675 (*vs*)	ν (γC−H)[a]; δ(COO)[b]
766 (*w*)	ν (γC−H)[a]
790 (*s*)	ν (γC−H)[a]
828 (*vs*)	ν (γC−H)[a]
872 (*m*)	ν (deform. mode vib.)[c]
902 (*m*)	ν ("*ring*" vibrat.)[d]
946 (*m*)	ν (COOH)[e]; ν ("*ring*" vibrat.)[d]
968 (*w*)	ν (ßCH)[f];
1070 (*m*)	ν (HC−OH, 2° alcohol)[g]
1120 (*w*)	ν (−C−O$^-$)[h]
1400 (*vw*)	ν (H−C−H)[i]
1500–1600 (*w*)	ν (N−H)[j];
1720 (*w*)	ν (C=O)[k];
2500–3550[l] (*m*)	ν (OH)[m]; ν (N−H, 2° amine)[m]

Band intensity: *w* – weak; *vw* – very weak; *m* – medium; *s* – strong; *vs* – very strong.

[a]C−H out-of-plane deformation vibration, (?C−H). These vibrations, in the substituted derivates of benzene, are in the interval from 680–1000 cm^{-1}.

[b]Deformation vibrations of the COO species within the carboxyl group (COOH) in L-adrenaline-D-hydrogentartrate.

[c]The spectrum of asymmetrically substituted benzene compounds shows a band? C−H (805–825 cm^{-1}) and a band originating from the deformation mode of the isolated hydrogen atom (870–885 cm^{-1}). The bands are medium or strong intensity.

[d]The carbon atoms, in benzene form an aromatic ring vibrating as a whole ("*ring*" vibrations). In the substituted compounds they show absorption in the 900–1025 cm^{-1} region, (*p-type* vibrations).

[e]This vibration is assigned to out-of-plane OH deformation vibration within carboxyl (COOH) groups.

[f]In-plane CH deformation vibrations, (ßCH). Aromatic compounds show bands in the spectral region 950–1225 cm^{-1}.

[g]These vibrations can be attributed to the presence of a 2° alcohol.

[h]This vibration can also be attributed to the secondary alcohol group.

[i]Vibrational band is attributed to deformation vibrations of the H−C−H group within L-adrenaline-D-hydrogentartrate. This vibrational band appears in the region 1340–1460 cm^{-1}.

[j]Possibly assigned to secondary amines with respect to deformation vibrations.

[k]This band is attributed to the C=O stretching vibration within the carboxyl group, COOH.

[l]Vibrational band in the 2500–3550 cm^{-1} region was observed with non-standard recording. Standard spectral recording covers the spectral region from 650 to 2000 cm^{-1}.

[m]Vibrational band is assigned to OH vibration in L-adrenaline-D-hydrogentartrate. The N−H group also absorbs in the same spectral region. Hydrogen bond frequencies can also be partially observed here.

Note: References [16, 18–20] were used for vibrational band identification.

changes were slightly more pronounced in the case of energy density of 1.70 J/cm^2. Typical features were: (i) the disappearance of the vibrational bands in the 910–1000 cm^{-1} region, especially bands at 946 and 968 cm^{-1}, (ii) the decrease in intensity of bands at 872 cm^{-1} and 1500–1600 cm^{-1} (the latter is attributed to N−H vibrations), and (iii) the slight increase of

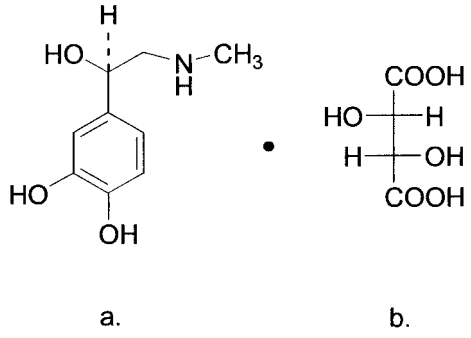

FIGURE 2 The component structure of L-adrenaline-D-hydrogentartrate. (a) Adrenaline; (b) Tartrate group.

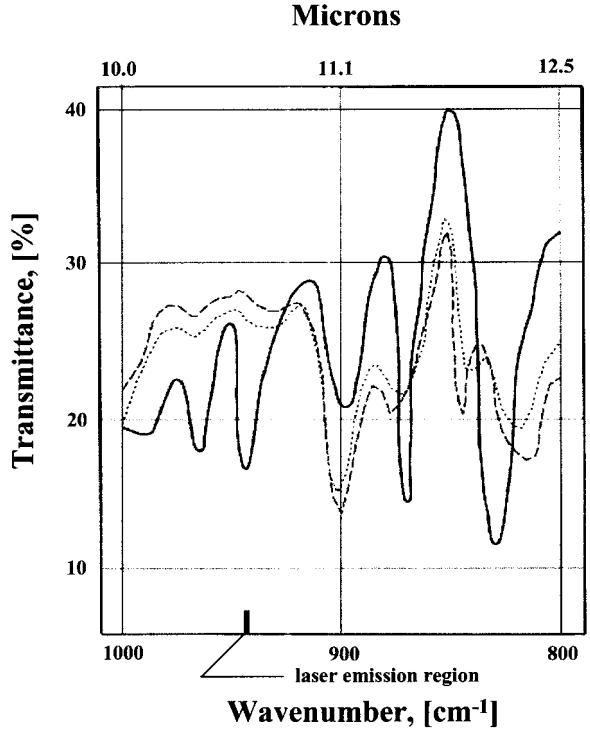

FIGURE 3 Infrared spectrum of L-adrenaline-D-hydrogentartrate in the spectral region 800–1000 cm^{-1} compared with spectra after carbon-dioxide TEA laser irradiation.
(—, before laser irradiation. – – –, - - -, after laser irradiation with 1.20 and 1.70 J/cm^2, respectively).

intensity of bands at 675 and 902 cm^{-1}. A new band appears at 815 cm^{-1}, but this is probably the result of a shift of the band at 828 cm^{-1}.

The chemical changes of L-adrenaline-D-hydrogentartrate obtained in the present experiment are obviously very complex. They can include decomposition of the compound; reaction of the compound with KBr matrices; reaction of the compound with ambient-gas, etc. The irradiation was performed in air, allowing for oxidation as well. A yellowish-white color was observed on the surface of L-adrenaline-D-hydrogentartrate pellet after cumulative action of 4000 laser pulses. Initial color of the sample was whitish-transparent. Modifications of the infrared spectra of L-adrenaline-D-hydrogentartrate incorporated in KBr matrices, Figures 1b and c, can lead to an assumption that the process is essentially of thermal nature.

L-adrenaline-D-hydrogentartrate is a grayish-white crystalline powder with a melting temperature in the interval from 147 to 152 °C. After this temperature interval the compound decomposes [16]. In order to prove/disprove the assumption that the laser action on L-adrenaline-D-hydrogentartrate incorporated in the KBr matrices is in essence a thermal effect, the thermal treatment of the sample was carried out. The thermal treatment was conducted at temperatures of 100 and 200 °C. For this purpose an electrical furnace with a reliable temperature control was used. The heating time was typically 3 h. For this experiment a new pellet (identical to the one that was laser irradiated) was made. The infrared spectra of L-adrenaline-D-hydrogentartrate incorporated in KBr matrices obtained after treatment at elevated temperatures are shown in Figure 4.

The features of the infrared spectra obtained after the thermal treatment are similar to those obtained after the laser treatment. Essential characteristics, Figure 4, including: (i) disappearance of vibrational bands in the 910–1000 cm^{-1} region, (ii) slightly increasing intensity of bands at 675 and 902 cm^{-1}, (iii) appearance of a band at 815 cm^{-1}, and (iv) drastic decrease of band intensity in the 2500–3550 cm^{-1} region, Table II.

The slight enhancement of the vibrational band intensity at about 680 cm^{-1}, see Figures 4b and 1a for comparison, leads to the conclusion that thermal decomposition of the sample, besides other effects, probably leads to decomposition of the tartrate group. A result of the decomposition can be the appearance of the CO_2 species, which exhibits absorption at about 680 cm^{-1}.

The broad band between 2500–3550 cm^{-1} spectral region, is attributed to OH vibrations in the L-adrenaline-D-hydrogentartrate. The N−H group also absorbs in the same spectral region. In this area of the spectrum frequencies from hydrogen bonds could also partially be observable [18]. At a temperature of 100 °C this band is drastically reduced, whereas at 200 °C it is

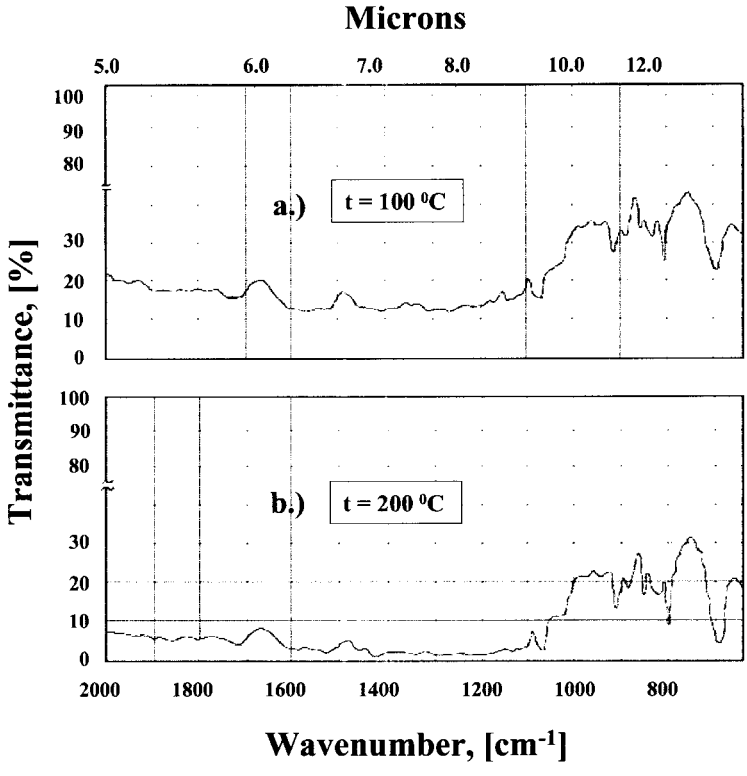

FIGURE 4 Infrared spectrum of L-adrenaline-D-hydrogentartrate after thermal treatment: (a) at a temperature of 100 °C and (b) 200 °C.

almost undetectable. This implies that OH groups were probably removed from the compound already at the first temperature, *i.e.* at 100 °C.

CONCLUSIONS

The laser energy densities of 1.20 and 1.70 J/cm^2 undoubtedly change the infrared spectra of L-adrenaline-D-hydrogentartrate incorporated in KBr matrices. The energy absorbed from the laser beam in the sample is apparently redistributed, generating effects such as: the enhancement of internal energy and decomposition of the compound. The observed changes in infrared spectra of L-adrenaline-D-hydrogentartrate indicate that the main causes of the modifications are thermal effects. The additional experiment of

sample thermal treatment, at elevated temperature, has confirmed this. The level of the pharmaceutical modification, induced by TEA carbon-dioxide laser radiation, showed a dependence on the laser energy density, number of accumulated laser pulses and temporal shape of pulse.

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