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A NOVEL THERMO-ACOUSTIC ANALYSIS TO DETECT PHOTOCHEMCIAL REACTION OF SALBUTAMOL

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ABSTRACT

A new thermo-acoustic analysis has been used to detect the photochemical reactions in salbutamol, a drug used as anti asthmatic/bronchodilator. Certain direct and derived acoustic parameters of pure medicine and that exposed to solar radiations have been determined as a function of temperature. Plots of these parameters versus temperature have been made. The nature of variation and the relative shift in the curves for the exposed samples compared with the unexposed ones have been used to study photochemical reactions. The results have been explained in the light of existing theories and confirmed using UV absorption spectra of the samples.

Key words: Thermo-acoustic analysis, Non-destructive method, Photochemical reaction, Salbutamol.

INTRODUCTION

Liquid medicines are usually kept in amber coloured bottles to protect from solar radiations. Direction may be given not to expose the medicine to direct sunlight in order to avoid photochemical reactions. But the time necessary for the occurrence of a photochemical reaction is very small. So the possibility of a photochemical reaction of the medicine due to sunlight or fluorescent light during the consuming process cannot be neglected. Moreover the UV A (320-400 nm) and UV B (290-320 nm) radiations from the Sun or a fluorescent lamp may penetrate the skin and may cause photochemical reactions on the medicine present in the blood circulation[1]. In the surgical operation theatre, powerful fluorescent lamps may be used to illuminate the wound. In this way,

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photochemical reaction can take place on the medicine circulating through the exposed blood vessels. So a knowledge of possible reaction of the sunlight on a medicine is helpful in taking necessary precautions during its usage. In the present work, thermo-acoustic analysis, a simple and non–destructive method compared with expensive and time consuming methods such as chromatographic, spectroscopic and enzymatic techniques, is made to study the photochemical reaction of a medicine salbutamol, a drug commonly used as bronchodilator, whose structure is shown –

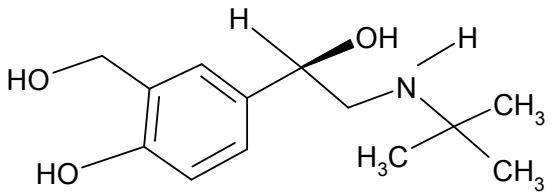


Fig. 1: Salbutamol $C_{13}H_{21}NO_3$

Salbutamol is a white crystalline powder soluble in methanol and ethanol and sparingly soluble in water. It is a beta 2- adrenergic bronchodilator known as Aerolin, Albuterl, Almotex, Asthalin etc. In the present work, we used the syrup known by the trade name Asthalin manufactured by Cipla. In thermo-acoustic analysis, the acoustical parameters of a liquid are plotted as a function of temperature. A pure liquid (single component or multi–component) has a characteristic curve depending on its chemical structure. Any deviation from this may be taken as an indication of change in chemical structure due to reaction induced by external agencies. This is the basic principle used in thermo-acoustic analysis. This method has been used successfully to distinguish between fructose and glucose (isomers having the same chemical composition), to detect and quantify the amount of fructose in coconut water[2] and to detect the adulteration of milk[3]. Sunlight is the most universal source of photochemical reactions especially in living organisms and in medicines. But sunlight is not available continuously and the spectral distribution and intensity vary from place to place and from time to time. Therefore, artificial sources are preferred[4,5]. Since we are interested only in the effect of solar radiation on the photochemical changes of the medicine, we used sunlight as the source of photochemical reactions.

EXPERIMENTAL

The pure unexposed medicine was taken as sample A, medicine exposed in scattered sunlight as sample B and that exposed in direct sunlight as sample C. The exposure time was fixed to 15 minutes from 11:00 to 11: 15 AM. The optical power of

scattered sunlight measured was 7.0 dB and that of direct sunlight was 27.2 dB. The measurements were done using an optical power meter manufactured by INFOS Model M-100. The density (ρ) and ultrasonic velocity (U) were determined at five different temperatures 298.15, 303.15, 308.15, 313.15 and 318.15 K for the pure medicine manufactured by Cipla (Sample A) and exposed medicines (samples B and C). The temperature was kept constant using a thermostatically controlled water circulating arrangement with an accuracy of ± 0.1 K. Density measurements were performed using a 12 cm^3 double stem pyknometer. Masses were measured using a single pan electronic balance with an accuracy of ± 0.1 mg. Ultrasonic velocities were determined by a single crystal ultrasonic interferometer (Mittal Enterprises Model No. F81) at a constant frequency of 2 MHz with an accuracy of ± 0.1 m/s. The derived acoustic parameters viz. Rao's specific sound velocity (r), adiabatic compressibility (β_s) and specific acoustic impedance (Z_A) were calculated using equations (1), (2), and (3). The UV absorption spectra of the samples A, B, and C were taken using a computerized UV-Visible spectrophotometer (UV win Lab, Lambda 25 UV/Vis, Perkin-Elmer Ltd, USA).

$$r = U^{1/3}/\rho \quad \ldots(1)$$

$$\beta_s = 1/U^2\rho \quad \ldots(2)$$

$$Z_A = U\rho \quad \ldots(3)$$

The units for r, β_s and Z_A are $Kg^{-1}\ m^{10/3}\ s^{-1/3}$, $Kg^{-1}\ m\ s^2$ and $Kg\ m^{-2}\ s^{-1}$, respectively.

RESULTS AND DISCUSSION

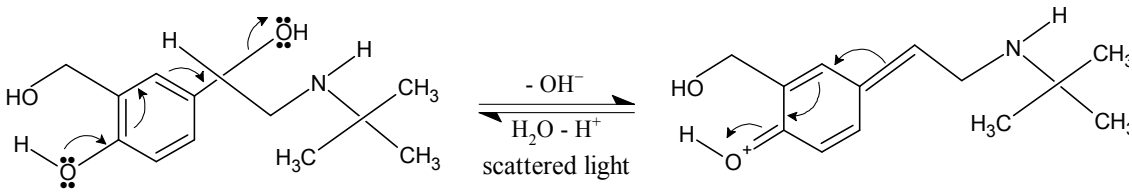
The UV absorption peaks of samples A, B and C are given in Table 1 and graphs plotted with U, ρ, β_s, r and Z_A versus temperature are shown in Figs. 1–3, respectively.

Table 1. UV absorption peaks of samples A, B and C

Sample A			Sample B			Sample C		
λ	**Absorbance**	**Type**	**λ**	**Absorbance**	**Type**	**λ**	**Absorbance**	**Type**
383.8	6.2496	peak	381.74	6.5953	peak	381.7	6.1703	peak
327.1	2.7198	peak	380.28	6.5032	peak	379.3	6.5107	peak
255.95	1.2335	peak	327.29	6.6057	peak	338.71	6.4589	peak
-	-	-	256.38	1.7319	peak	327.26	6.7523	peak
-	-	-	204.74	6.4241	peak	256.16	1.2215	peak

In the UV absorption spectrum of the pure unexposed salbutamol (Sample A), absorption peaks are obtained at 255.95 nm, 327.10 nm and 383.80 nm. These are due to the $\pi \rightarrow \pi^*$ transition. 255.95 nm accounts for the presence of benzene nucleus in the compound and 327.10 nm accounts for the presence of meta-xylene skeleton in the compound. The unshared electron pair present in the phenolic OH group is in conjugation with the π electrons of the benzene nucleus and it can take part in resonance stabilization. The lone pair in the phenolic group contributes mainly to resonance in the excited state resulting in a decrease of energy in the excited state. The energy required to raise the molecule from its ground state to excited state is relatively small and consequently absorption takes place at longer wavelength. Hence, an absorption peak at about 383.80 nm is observed.

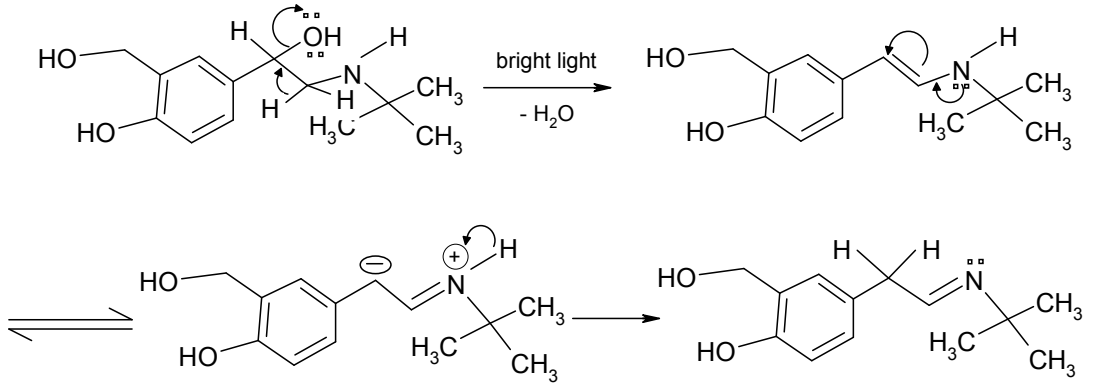
For salbutamol exposed to the scattered sunlight entering through an open window of the laboratory (sample B), absorption peaks are obtained at 381.74 nm, 380.28 nm, 327.29 nm, 256.38 nm and 204.74 nm. The absorption peaks are due to $\pi \rightarrow \pi^*$ transition. The absorption peak at 256.38 nm is due to the benzene ring. The peak at 327.29 nm is due to the presence of meta-xylene skeleton. The peak at 381.74 nm is due to the conjugation of OH group with the π electrons of the benzene nucleus as explained earlier. The new peak obtained at 380.28 nm is due to the quinonoid ring formed during the exposure to scattered sunlight. The unshared electron pair during the exposure takes part in delocalization with the benzene nucleus forming a quinonoid ring by the temporary elimination of water and the irradiation process is found to be reversible and an equilibrium is established. The energy of interaction is relatively small and consequently absorption takes place around 380.28 nm.



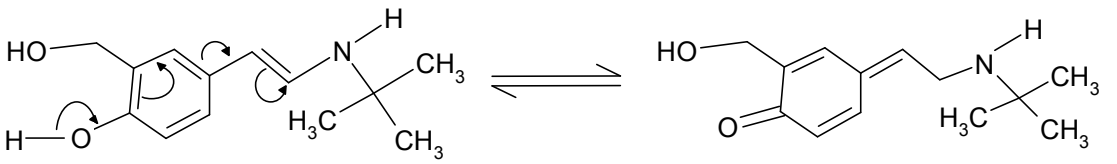
The chemical reaction of salbutamol due to scattered sunlight

For salbutamol exposed to direct sunlight (sample C), absorption peaks are obtained at 381.70 nm, 379.3 nm, 338.71 nm, 327.26 nm and 256.16 nm. During exposure to bright light, the lone pair on the phenolic group is involved in delocalization and a quinone nucleus is transiently formed. The energy required to raise the molecule from its ground state to excited state is relatively small and absorption takes place at a longer

wavelength. The formation of quinone nucleus on exposure accounts for the characteristic absorption around 379.3 nm. The absorption at 381.7 nm is due to the conjugation of phenolic group with π^- electrons of the benzene nucleus. The absorption peak at 327.26 nm is due to the $\pi \rightarrow \pi^*$ transition due to meta–xylene skeleton. The peak at 256.16 nm is due to the $\pi \rightarrow \pi^*$ transition mainly due to the benzene nucleus.



(a)



(b)

Chemical reactions of salbutamol due to the direct sunlight

When exposed in direct sunlight, there is a possibility of elimination of a water molecule transiently producing C = C bond and since the lone pair on the nitrogen atom is in conjugation with the newly formed double bond, which can take part in delocalization producing a dipolar structure as a result of resonance. Combination of the resonating form of the molecule give rise to splitting of the ground state into two different levels, which do not differ widely in energy. The transition from the lower to the upper of these levels would give an absorption of radiation at longer wavelength, That is absorption around 338.7 nm.

In Fig.1 (a), the ultrasonic velocity U is plotted as a function of temperature for the samples A, B and C. For sample A, the rate of rise of slope is small from 303 to 308 K. Below 303 K and above 308 K, the slope is higher. There is a dip at 308 K and a peak at

303 K. This is the characteristic thermal response of ultrasonic velocity U for salbutamol syrup. For sample B, that is the syrup exposed in the scattered sunlight, the thermal response curve of U has all the portions similar to the one present in sample A but shows a small upward shift and small variations of slope at different portions. The peak at 303 K and the dip at 308 K get amplified a little from that of A. There is a greater slope from 298 to 303 K. These small variations are due to the small chemical changes in the medicine due to the photochemical reaction in scattered sunlight. This is verified using the UV spectrum of the samples. During the irradiation with the scattered light, the non-bonding electron on the phenolic group take part in delocalization with the π electrons of the benzene nucleus creating quinonoid ring transiently and the energy difference between HOMO and LUMO is lowered shifting to higher wavelength and the electronic transition probability is also increased. But this change is only upon scattered light irradiation and is not permanent and hence, the deviation from the parent compound is comparatively small.

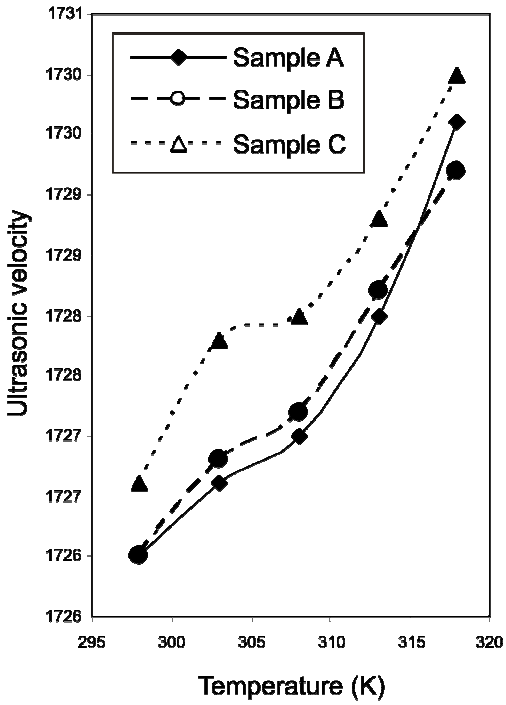


Fig. 1 (a): Variation of ultrasonic velocity U with temperature for samples A, B and C

For sample C, that is the syrup exposed in the direct sunlight, the thermal response curve of U has all the portions similar to that of sample A but shows a larger upward shift and larger change in slope. The peak at 303 K and the dip at 308 K are magnified to a

greater extent. The slope of the curve is increased very much from 298 K to 303 K and decreased considerably from 303 K to 308 K. The slope between 308 K and 318 K remains the same as for the sample B. This larger variation of the thermal response curve is due to the comparatively strong photochemical reaction of the medicine due to the direct sunlight which is verified using UV spectrum. During the action of bright sunlight, there is a possibility of elimination of water temporarily producing a double bond, which is in conjugation with the unshared electron pair on the nitrogen atom and this unshared electron pair gets involved in conjugation with the π electrons of the double bond producing partial dipolar nature. Furthermore, the unshared electron pair is also involved in delocalization with the π^- electrons of the benzene nucleus, creating a quinonoid ring and this is greater than that with scattered light irradiation. Thus, the energy difference between HOMO and LUMO is lowered, shifting to higher wavelength. The transition probability is also increased. In Fig.1 (b), the density of the medicine is plotted as a function of temperature for samples A, B and C. For sample A, there is a large negative slope from 298 to 308 K and from 313 K to 318 K. Between 308 and 313 K, the negative slope is very small. There is a dip at 308 K and a peak at 313 K. This is the characteristic thermal response of density ρ for the medicine salbutamol.

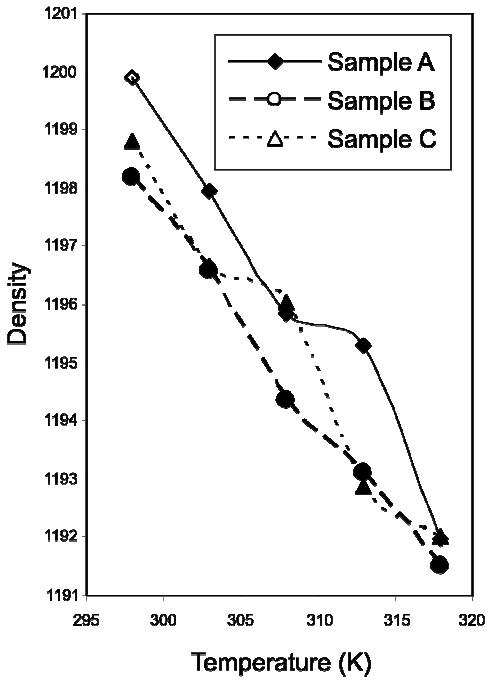


Fig. 1 (b): Variation of density ρ with temperature for samples A, B and C

For the sample B, thermal response curve of ρ has all the three portions present as in sample A, but shows a downward shift and small variations of slope. From 298 K to 308 K, the slope of B is the same as A. Between 308 and 313 K, the slope is greater than that of sample A and beyond 313 K, the slope is less than that of A. The dip at 308 K and the peak at 313 K becomes smooth. Therefore, the thermal response of B has only a small variation of slope from A with a shift, which indicates a small chemical change with no considerable change in the general structure of the medicine as verified by the UV spectrum.

The thermal response of sample C is quite different from A and B. It has got two dips at 303 K and 313 K and a peak at 308 K. The negative slope is high from 298 K to 303 K and from 308 K to 313 K. The slope is very small from 303 to 308 K and beyond 313 K. The thermal response of C has got a horizontal shift of 5 K (phase difference of 5 K). The larger variation of thermal response of C indicates the occurrence of a comparatively strong photochemical reaction of the medicine in direct sunlight. The wavelike nature of thermal variation indicates the increased activity of the compound which is verified by the UV spectrum.

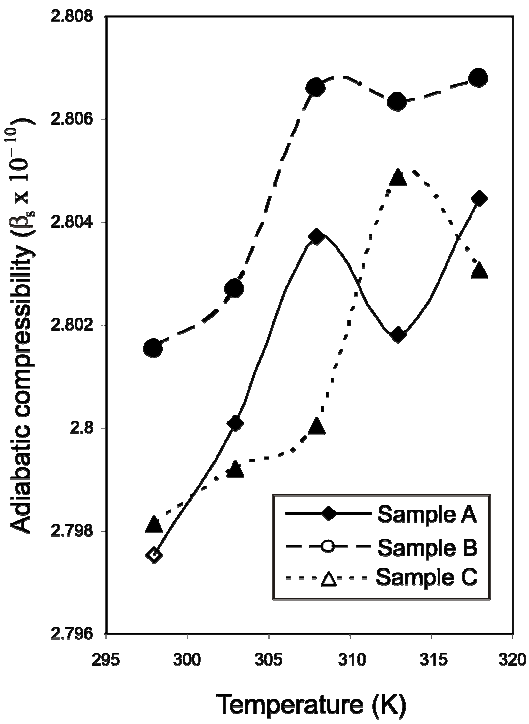


Fig. 2 (a): Variation of adiabatic compressibility β_s with temperature for samples A, B and C

In Fig. 2 (a), variation of the adiabatic compressibility β_s is plotted as a function of temperature for samples A, B and C. For sample A, the curve has a positive slope from 298 to 308 K and beyond 313 K. Between 308 K and 313 K, it has a negative slope. There is a peak at 308 K and a dip at 313 K. This is the characteristic thermal response of β_s for salbutamol. For sample B, even though the curve has all the portions present as in sample A, at their respective temperatures, the graph is shifted upwards and becomes smooth a little. The wavelike thermal response has undergone damping. The shift and variation of slope of the curve are due to the photochemical change of the medicine in the scattered sunlight. Since there is no drastic change in the shape of the curve, it is evident that photochemical reaction does not change the fundamental chemical structure of the medicine but had a slight modification only. The thermal response β_s for sample C is quite different. It has a peak at 313 K and dip at 308 K. The curve is roughly similar to A but having a shift of 5 K in the X- direction (phase difference of 5 K). Thus for C, the positions of peak and dip of A get interchanged. This larger variation of the thermal response of C is due to the comparatively strong photochemical reaction of the medicine in the direct sunlight.

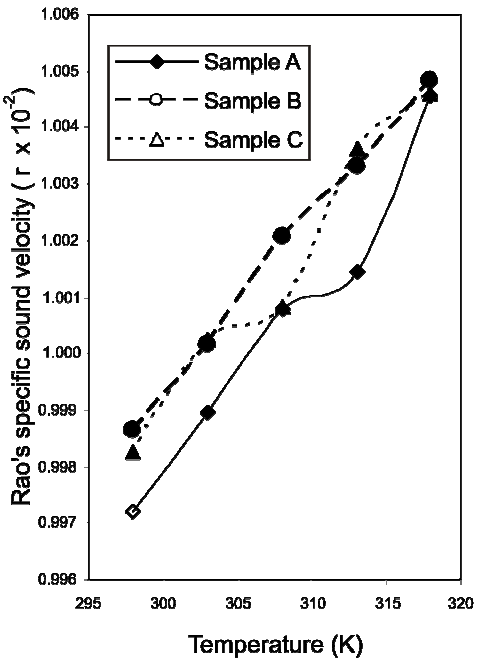


Fig. 2(b): Variation of Rao's specific sound velocity (r) with temperature for samples A, B and C

In Fig. 2(b), Rao's specific sound velocity (r) of the medicine is plotted as a function of temperature for samples A, B and C. For sample A, there is a large positive slope from 298 to 308 K and from 313 to 318 K. Between 308 and 313 K, the positive slope is very small. There is a peak at 308 K and a dip at 313 K. This is the characteristic thermal response of R for the medicine salbutamol. For sample B, thermal response curve of r has all the three portions present in sample A but shows an upward shift and small variations of slope. From 298 to 308 K, the slope of B is the same as A. Between 308 and 313 K, the slope is greater than A and beyond 313 K, the slope is less than A. The peak at 308 K and dip at 313 K becomes smooth. Therefore, the thermal response of B has only a small variation of slope from A with a shift, which indicates a small chemical change with no considerable change in the general structure of the medicine. The thermal response of sample C is quite different from A and B. It has got two peaks at 303 K and 313 K and a dip at 308 K. The slope is higher from 298 to 303 K and from 308 to 313 K. The slope is very small from 303 to 308 K and beyond 313 K. The larger variation of thermal response of C from A indicates the occurrence of a comparatively strong photochemical reaction of the medicine in direct sunlight.

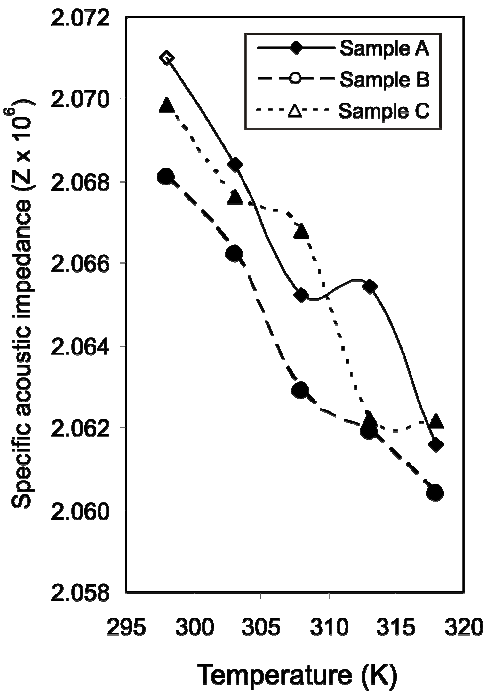


Fig. 6: Variation of specific acoustic impedance Z_A with temperature for samples A, B and C

In Fig. 3, variation of specific acoustic impedance (Z_A) is plotted as a function of temperature for samples A, B and C. For sample A, the curve has a negative slope from 298 to 308 K and beyond 313 K. Between 308 and 313 K, it has a positive slope. There is a dip at 308 K and a peak at 313 K. This is the characteristic thermal response of Z_A for salbutamol. For sample B, even though the graph has all the portions present in A at their respective temperatures, the curve is shifted downwards and becomes smooth a little. The wavelike thermal response has undergone a damping. The shift as well as the variation of the slope of the curve is due to the photochemical change of the medicine in the scattered sunlight. Since there is no drastic change in the shape of the curve, it is evident that there is no considerable change in the chemical structure of the medicine due to scattered light but it had a slight modification only.

The thermal response of Z_A for sample C is quite different from A and B. It has a peak at 308 K and a dip at 313 K. The curve is roughly similar to A but having a shift of 5 K in the X- direction (phase difference of 5 K). Thus for C, the positions of peak and dip of A get interchanged in temperature. This larger variation of the thermal response of C is due to the comparatively strong photochemical reaction of the medicine in the direct sunlight

The HOMO and LUMO values of samples A and C are calculated theoretically using Gaussian03 program package at the HF level[6]. The values obtained are - 0.307 (HOMO), 0.150 (LUMO) for sample A and - 0.324 (HOMO), 0.042 (LUMO) for sample C. The calculated energy difference between LUMO and HOMO is in agreement with the observed experimental results.

The thermal responses of the acoustic parameters of the medicine salbutamol are characteristic curves. The temperatures are selected in such a way that human body temperature lies within the range. The slight change in the structure due to scattered light appears as a slight change in shape and small shift in thermal response of sample B. Similarly the strong photochemical change in the structure due to direct sunlight produces a larger change in slope and larger shift in the thermal response of sample C. Thus it is concluded that thermo-acoustic analysis is a powerful tool to detect and compare the photochemical change in the structure of medicines in a non-destructive way using ordinary non-sophisticated instruments.

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