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A Novel thermo-optic analysis to detect photochemical reaction of salbutamol

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ABSTRACT

A new thermo-optic analysis has been used to detect the photochemical reactions in salbutamol, a drug used as anti asthmatic/bronchodilator. Certain derived optic 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.

Keywords: Thermo-optic analysis, non destructive method, photochemical reaction, salbutamol**.**

INTRODUCTION

To protect from solar radiations Liquid medicines are usually kept in amber coloured bottles. Direction may be given not to expose the medicine in 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 (320-400nm) and UV B (290-320nm) radiations from the sun or a fluorescent lamp may penetrate the skin and may cause photo-chemical reactions on the medicine present in the blood circulation[1]. So a knowledge of possible reaction of the sunlight on a medicine is helpful in taking necessary precautions during the usage of it .In the present work, Thermo-optic analysis, a simple and non destructive method compared with expensive and time consuming methods such as chromatographic, spectroscopic and enzymatic techniques, is done to study the photochemical reaction of a medicine Salbutamol, a drug commonly used as bronchodilator whose structure is shown in Fig.1.

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.

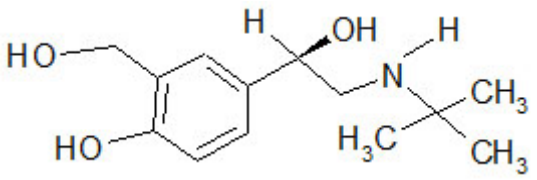

Fig.1: of Salbutamol $C_{13}H_{21}NO_3$

In the present work we used the syrup known by the trade name Asthalin manufactured by Cipla. In thermo-optic analysis, the optical 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 the chemical structure of it. 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-optic 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 time to time. Therefore artificial sources are preferred[4]. 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 refractive index (n) 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 & 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. The refractive index was measured using Abbe refractometer with an accuracy of ± 0.0001. Specific optical volume v and Specific optic impedance Z_o were calculated using equations 1 and 2. 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).

$$v = n/\rho^{0.45} \quad ...(1)$$

$$Z_0 = 120\pi\rho/n \quad ...(2)$$

(where n is the refractive index and ρ is the density).

The derived optic parameters v and Z_o are plotted against temperature for pure medicine and the medicine exposed to sunlight. The nature of variation and the relative shift in the curves for exposed samples from the unexposed one have been used to detect the photo physical change and hence the change in the activity of the drug. The results are explained using the UV absorption spectra of the pure and light exposed drugs.

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

Sample A		Sample B		Sample C	
Abscissa	Ordinate	Abscissa	Ordinate	Abscissa	Ordinate
383.80	6.2496	381.74	6.5953	381.70	6.1703
327.10	2.7198	380.28	6.5032	379.30	6.5107
255.95	1.2335	327.29	6.6057	338.71	6.4589
-	-	256.38	1.7319	327.26	6.7523
-	-	204.74	6.4241	256.16	1.2215

RESULTS AND DISCUSSION

The UV absorption spectra peaks of samples A, B and C are given in table 1 and graphs plotted with v and Z_o versus temperature are shown in Fig. 4.

In the UV absorption spectrum of the pure unexposed Salbutamol, (Table 1), absorption peaks are obtained at 255.95 nm, 327.1 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. 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 381.84 nm is due to the conjugation of OH group with the electrons of the benzene nucleus as explained earlier. The new peak obtained at 380.28nm is due to the quinonoid ring formed during the exposure to scattered sunlight. The unshared electron pair during the exposure take part in delocalization with the benzene nucleus forming a quinanoid ring by the temporary elimination of water and the irradiation process is found to be reversible and an equilibrium as given in fig.2 is established. The energy of interaction is relatively small and consequently absorption takes place around 380.28 nm.

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 as explained earlier. 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.

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 as shown in fig.3. 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.

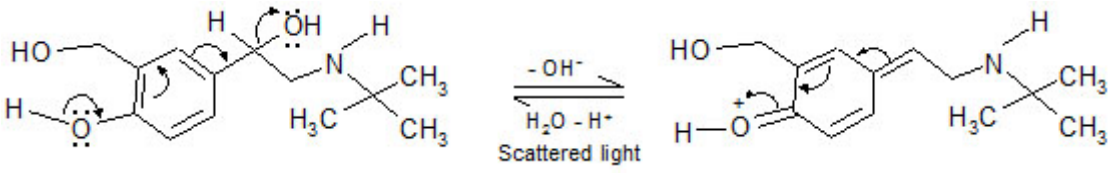

Fig. 2: The chemical reaction of Salbutamol due to scattered sunlight

In fig.4 (a), the Specific optic volume is plotted as a function of temperature for the samples A, B and C. For sample A, the graph is having a positive slope below 307K and above 313 K. From 307 K to 313 K, It has a negative slope. There is a characteristic peak at about 307 K and a dip at 313K.

Sample B has a positive slope up to 308 K followed by a negative slope. The peak value of specific optic volume is obtained at 308 K. These small variations are due to the small chemical change of 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.

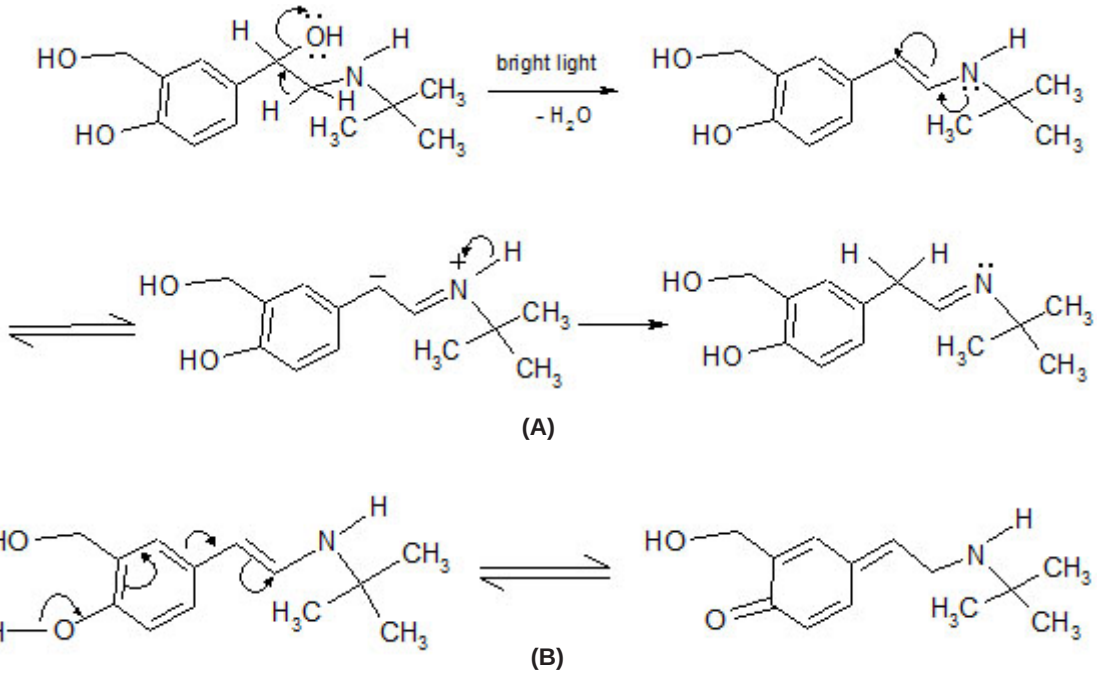

Fig. 3: Chemical reactions of salbutamol due to the direct sunlight.

Sample C has got two regions of positive slope and two regions of negative slope. Two peaks are there corresponding to 303 K and 313 K and a dip at 308 K. 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 the 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 get involved in conjugation with the electrons of the double bond producing partial dipolar nature. Furthermore the unshared electron pair 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.4(b), the Optic impedance Z_o 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 to308 K and from313 K to 318 K. Between 308 and 313 K, the slope is positive. There is a dip at 308 K and a peak at 313 K. This is the characteristic thermal response of Optic impedance Z_o for the medicine Salbutamol.

For the sample B, thermal response curve of Z_o has all the three portions present as in sample A but shows a downward shift. Beyond 308 K, the variation of slope becomes small. The dip at 308 K and the peak at 313 K of the unexposed medicine become smooth due to the exposure in the scattered light. Therefore the thermal response of B has only a small variation of slope from A with a shift which

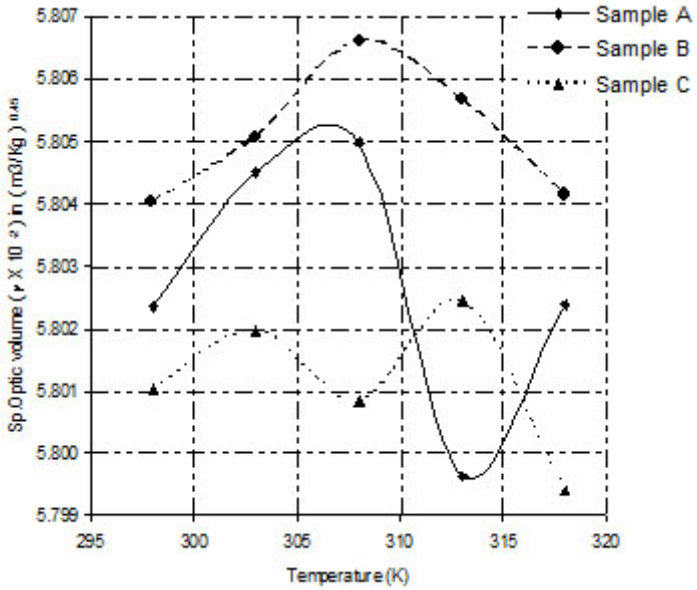

Fig. 4(a): Variation of Specific optic volume with temperature for samples A, B and C

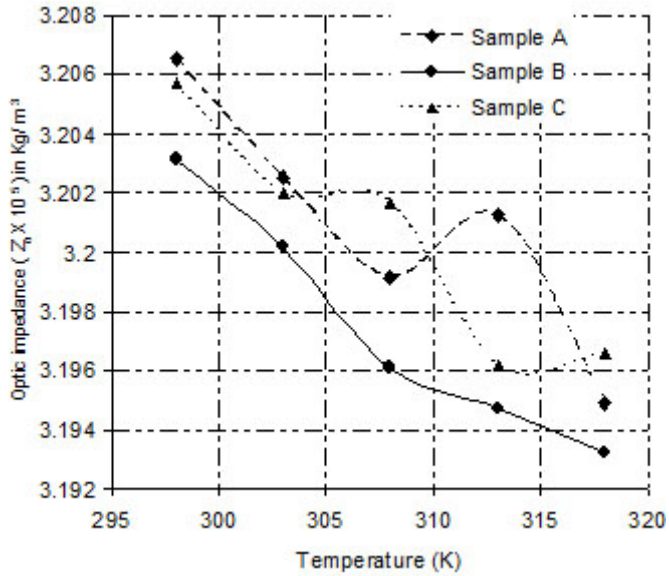

Fig. 4(b): Variation of Optic impedance Z_o with temperature for samples A, B and C

indicates a small chemical change with no considerable change in the general structure of the medicine which is 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.

The HOMO and LUMO values of samples A and C are calculated theoretically using Gaussian03 program package at the HF level[5]. 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.

REFERENCES

1. Cosa. G, *J. Pure Appl. Chem*., **76(2)**: 263 (2004).
2. Mohanan., S, Iype., L, Laila., M, Thomas Panicker.P.G, Bindu.R.G and Domini.L, *J. Acoustic Lett*., **24(9)**: 171 (2001).
3. Mohanan., S, Thomas Panicker., P.G, Iype., L, Laila, M, Domini, L. and Bindu. R.G, *Pramana-J. Phys*., **59(3)**: 525 (2002).
4. Kagan., J, *Organic Photochemistry: Principles and Applications*, Academic Press Ltd, London, (1993).
5. Frisch, M.J., *et al.* Gaussian03 , Gaussian Inc, Wallingford CT (2004).