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Spectroscopic Investigation and Qualitative Analysis on Some Anti-Malarial Drugs Primaquine Phosphate and Chloroquine Phosphate

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Abstract: *The spectroscopic investigation on the samples of Primaquine Phosphate and Chloroquine phosphate which are widely used as antimalarial drugs. The FTIR spectra of these samples were recorded in the region 4000 - 400 cm⁻¹. The band assignment was carried out for the fundamental modes of vibration. To find the ideal storage condition for primaquine phosphate and chloroquine phosphate, the UV-visible spectra of these drugs, subjected to different conditions of storage, were recorded in the 200-600 nm regions. From the recorded spectra, it has been concluded that Primaquine phosphate and Chloroquine phosphate should be stored under room temperature condition only. Subjecting them to other conditions like sun light, Gamma rays etc. will decrease the effectiveness of the drug.*

Keywords – *Anti-malarial drugs, Chloroquine Phosphate, Primaquine Phosphate, Fourier Transform Infrared Spectroscopy and UV-Visible spectroscopy.*

I. INTRODUCTION

Infrared spectroscopic methods are being extensively used to identify the structural groups present in a compound. Suther and his co-workers (1) suggested an interesting method of assigning group frequencies observed in vibrational spectra. In the recent past, extensive work has been carried out by Gunasegaram and his co-workers (2-8) on samples of pharmaceutical importance. A detailed, spectral interpretation pseudoephedrine hydrochloride (PEH) has been carried out using Fourier Transform Infra Red Spectroscopy (2). The infrared spectra of Phenyl Propanol amine hydrochloride (PPAH) have been thoroughly investigated and a detailed vibrational band assignment attempted (3). The infrared spectrum of theophylline has been recorded and analysed (4), to study its structure. The assignment of the fundamental frequencies is made on the basis of magnitude and relative intensities of the observed bands and the assignments of C-H, C=H, C=O, C=C, C-C, have been discussed. A qualitative discussion on the infrared band frequencies of atonal (5) has been made in analogy with the assignments of related compounds. Spectral investigation on Tetracycline and Ampicillin has been carried out with respect to their characteristic group vibrations. (6) The ultraviolet absorption spectra of blood samples from diseased subjects and also blood samples from normal healthy subjects belonging to the same blood group, age and sex were analysed (7). It was observed that the absorption spectra of the diseased blood show marked changes from that of the normal blood showing the manifestation of the disease. Recently UV-VIS spectroscopic method has been employed successfully to study the effectiveness of PPAH (8). The variations of the absorbance of the λ_{max} of the drug subjected to sunlight, UV radiations, IR radiations and also at different temperature conditions have been analysed (9). UV-Visible spectroscopic methods have been employed to investigate samples of biological interest (6,7). The spectroscopic method is a proven one in the analysis of drugs and hence it has been established that the sophisticated spectrophotometers can be used as powerful tools for quality control in pharmaceutical laboratories. During the course of investigation on some pharmaceutical and biological materials, our attention has been turned towards Primaquine phosphate and Chloroquine Phosphate in the present work.

Though Primaquine Phosphate and Chloroquine Phosphate were widely used for treating malaria, a detailed spectral investigation has not been so far made on the compounds. In the present work, Fourier Transform Infrared and UV-VIS spectroscopic methods have been employed successfully to study the samples and the results are discussed.

II. PHARMACEUTICAL DATA AND SIGNIFICANCE OF THE SPECTRAL MEASUREMENT ON PRIMAQUINE PHOSPHATE AND CHLOROQUINE PHOSPHATE

Pharmaceutical Science is a part of general pharmacology. It is concerned with the identification, selection, presentation and standardization of drugs. The drugs can be prescribed in the form of ointment, injection and tablets, but whatever be the form of the drug, its function is to cure the disease for which it is prescribed. The pharmaceutical data of primaquine phosphate and chloroquine phosphate are given in Table 1.

Table 1 - Pharmaceutical data of Primaquine Phosphate and Chloroquine Phosphate

Characters	PHARMACEUTICAL DATA	
	Primaquine Phosphate	Chloroquine Phosphate
Molecular formula	$C_{15}H_{21}N_3O, 2H_3PO_4$	$C_{18}H_{26}N_3, 2H_3PO_4$
Molecular weight	455.34	515.87
Category	Antimalarial	Antimalarial antiamor
Dose	Dose: 15 mg once a day for 14 days	Dose: 300 to 450 mg daily or twice a weak
Solubility	Orange, crystalline powder, odourless	White or almost white crystalline powder, odourless
Identification	Soluble in H_2O insoluble in ethanol and ether	Freely soluble in H_2O very slightly soluble in chloroform
Maximum λ_{max}	260 nm	245nm

A qualitative analysis on drugs is used to determine the occurrence of additives or impurities present in the drugs, because of various causes as mentioned above. It should be made by using highly sophisticated instruments like UV-VIS and FTIR spectrometers. The sample should be analysed before marketing it and its quality factor should be determined in terms of the fundamental absorption bands in IR spectrum. Hence, the present work is aimed to make a through investigation on the quality factor of primaquine phosphate and chloroquine phosphate by UV-VIS and infrared spectroscopic methods.

III. FTIR SPECTRA AND VIBRATIONAL BAND ASSIGNMENT

The samples of primaquine phosphate and chloroquine phosphate were obtained from a reliable source and were used as such. The FTIR spectrum of the samples were recorded in the $4000-400\text{ cm}^{-1}$ region using Bruckner IFS 66V double beam spectrophotometer. The spectra recordings were carried out at RSIC, IIT, Chennai, India under identical conditions by KBr pellet technique. The FTIR spectra are recorded and their observed frequencies and their band assignments are summarized in Table 2 and 3.

Table 1 - Vibrational band assignments on primaquine phosphate

Frequency	Intensity	Vibrational Band Assignment
430	MS	C-C-C out of plane bending
460	MS	C=C out of plane bending
525	VS	C-C out of plane bending
576	MS	C-H out of plane bending
669	W	C-H out of plane bending
770	W	C-N Stretching
830	W	C-H out of plane bending
872	MS	C-C stretching
988	VS	P-O.Sing breathing
1058	VS	P-O.Asym. Str
1134	VS	C-O Stretching
1170	MS	C-N Stretching

1368	W	N-H bend
1385	W	C-C Stretching
1450	W	C-C Stretching
1517	VW	C-C Stretching
1600	VW	C-N Stretching
1649	W	CN Stretching
2929	VW	Symmetric C-H stretching
3100	W	Asym C-H stretching
3090	W	Aromatic C-H sym str
3150	W	Aromatic C-H sym str
3295	W	Aromatic C-H Stretching
3427	W	O-H/N-H Stretching
3530	W	NH ₂ Symmetric stretching.

Table 2 - Vibrational band assignments on Chloroquine phosphate

Frequency	Intensity	Vibrational Band Assignment
420	W	C-C out of plane bending
467	W	C-C out of plane bending
539	W	C-C out of plane bending
656	VVW	C-H out of plane bending
750	VVW	C-H out of plane bending
800	VW	C-N Stretching
910	MS	C-H in plane bending
942	S	C-H in plane bending
1000	S	P-O stretching asym. str
1061	S	P-O stretching asym. str
1075	MS	C-C stretching
1150	MS	C-N stretching
1211.5	W	C-H in plane bending
1242.0	VW	C-H in plane bending
1368.0	VW	CH ₃ stretching
1420.0	VW	CH ₂ /CH ₃ asymmetric bending
1458.0	MS	CH ₃ asymmetric bending
1551.8	MS	C-C stretching
1558.0	S	C-N stretching
1612.0	VS	C-C ring stretching
2700.0	VW	Symmetric C-H stretching of methyl group
2770.0	VW	Symmetric C-H stretching of methyl group
2940.0	W	Asymmetric C-H stretching of methyl group
3100.0	VW	Aromatic C-H stretching
3230.0	VW	Aromatic C-H stretching
3427.0	W	N-H stretching

S – Strong; MSW- Medium Strong ; VS-Very Strong ; W – Weak ; VW - Very Weak ; VVW - Very Very Weak

Infrared and Raman spectroscopic methods are used to identify the structural groups in a compound. Sutherland and his co-workers (1) suggested methods of assigning group frequencies as position intensity and width of the bands and also the behaviour of the band under dilution. It is evident from the molecular structure of primaquine phosphate and chloroquine phosphate that the two compounds are

benzene derivatives. Besides phosphate group is present in both the samples. Therefore their FTIR spectra analysis has been carried out based on benzene and its derivatives besides samples containing phosphate group.

A. C-H Stretching

Generally aromatic C-H stretching vibrations occur in the region of $3000 - 3100 \text{ cm}^{-1}$. Most of mononuclear and poly nuclear aromatic compounds show three or four peaks in the region $3010 - 3080 \text{ cm}^{-1}$. C-H stretching vibrations of benzene occur at 3061 cm^{-1} , 3048 cm^{-1} and 3080 cm^{-1} . Of these three, last two are degenerate and each of them gives rise to two bands in substituted benzene compounds (12). In the present case for Primaquine Phosphate the C-H symmetric stretching vibration occurs at 3090 cm^{-1} . The corresponding asymmetric stretching is seen as a band at 3150 cm^{-1} for Chloroquine Phosphate

B. C-H Deformations

The C-H bending vibrations appear at two distinct regions $1300 - 1000 \text{ cm}^{-1}$ and $700 - 610 \text{ cm}^{-1}$ (13). The first region may be due to C-H in plane bending vibration and the region is due to C-H out-of-plane bending vibration. In the FTIR spectrum of H.P., the band at 872 cm^{-1} is assigned to C-H in-plane bending vibration while the bands at 669 cm^{-1} and 770 cm^{-1} are assigned as C-H out of-plane bending vibrations.

C. C-C Stretching vibrations

In substituted benzene, the C-C stretching vibrations are derived from the four C-C stretching modes 1595 cm^{-1} ; 1485 cm^{-1} , 1311 cm^{-1} and 992 cm^{-1} of benzene, out of which the first two are double degenerated (9, 10). The C-C stretching vibrations in the spectrum of P.P. is seen as a band at 1385 cm^{-1} . Earlier workers have pointed out that a band around 1000 cm^{-1} is invariably observed in mono-substituted, meta-substituted and symmetrical trisubstituted benzene. Previous authors have assigned this frequency as breathing mode of benzene ring in which carbon atoms at 2,4,6 positions are radially displaced, while the other three atoms remain at rest. Wiffen (11) has showed this mode as p-mode in the case of mono-halogenated benzenes. For P.P., the intense band at 988 cm^{-1} is assigned to the breathing mode of the ring. This is in good agreement with the reported values (11, 14).

D. C=C stretching vibrations

Due to skeletal vibrations, there are two or three bands in the region $1625-1430 \text{ cm}^{-1}$ for aromatic six membered rings viz., benzene and pyridines. These bands arise due to ring carbon stretching vibrations (15). In the present investigation, the ring is conjugated. For substituted benzene with identical atoms or groups on all prepares of ring carbon atoms, the vibrations causing the band at $1625-1590 \text{ cm}^{-1}$ are infrared inactive, due to symmetry consideration. Conjugated ring structures normally exhibit a doublet in their IR spectra in the 1500 cm^{-1} region (15). The doublet observed at 1450 cm^{-1} and 1517 cm^{-1} is assigned to C=C stretching vibrations.

E. Ring Vibrations

Literature on the work of benzene and its derivatives reports that the ring carbon-carbon stretching vibrations occur in the region $1625-1530 \text{ cm}^{-1}$ (15, 16). For six member ring, two or three bands in this region arise due to skeletal vibrations. In general, the bands of variable intensity are observed at $1625-1590 \text{ cm}^{-1}$, $1590-1575 \text{ cm}^{-1}$, $1525-1470 \text{ cm}^{-1}$ and $1465-1430 \text{ cm}^{-1}$ for substituted benzene. The above statement the band observed at 1649 cm^{-1} assigned to carbon ring stretching. The ring C-C stretching vibration is seen as a band at 1550 cm^{-1} in the spectrum of Primaquine Phosphate.

The bands in the aromatic ring deformation region are quite sensitive to the change in the nature and position of substituents. Although other bands depend mainly on the distribution and number of substituents rather than on their chemical nature or mass. So these latter vibrations of the ring of hydrogen atoms are extremely useful in determining the position of substituents (17, 18). For mono substituted aromatics, the bands due the out-of-plane ring deformation vibration occur in the region $410-550 \text{ cm}^{-1}$. In the present investigation C-C-C deformation occurs at 430 cm^{-1} , out-of-plane C=C deformation occurs at 460 cm^{-1} and C-C out-of-plane bending occurs at 525 cm^{-1} and 576 cm^{-1} .

F. Methyl Group Vibrations

Bands of medium intensity observed in the $2900 - 2700 \text{ cm}^{-1}$ region due to symmetric and asymmetric stretching vibrations of methyl group. The band at 2929 cm^{-1} in the spectrum of Primaquine Phosphate is assigned to C-H symmetrical stretching and the band around 3100 cm^{-1} to asymmetric C-H stretching vibration of methyl group.

G. C-N Vibrations

In primary, secondary and tertiary amines, medium to weak absorption bands for C-N linkage appear in the region $1250-1020\text{ cm}^{-1}$. The vibrations responsible for these bands involve C-N stretching coupled with stretching of adjacent bonds in the molecule. The position of absorption in the region depends on the class of amines and pattern of substitution on the carbon. In the present case, the bands at 830 cm^{-1} and 1170 cm^{-1} are due to C-N stretching vibrations.

H. C=N stretching

Interaction between ring C=C and C=N stretching vibrations result in two medium intensity absorption about 100 cm^{-1} apart. These absorption occur in the $1615-1575\text{ cm}^{-1}$ and $1520-1465\text{ cm}^{-1}$ regions. A band is usually observed in the region $1000-985\text{ cm}^{-1}$ but this band may be very weak or undetectable for 3-substituted pyridines in the present case, C=N stretching vibration is observed as a band at 1649 cm^{-1} .

I. N-H vibration

Primary and secondary amides show sharp bands in the $3400 - 3300\text{ cm}^{-1}$ and $1650-1515\text{ cm}^{-1}$ region (12). Yutaka et al have assigned NH stretching vibration to 3320 cm^{-1} band in his work (19). In the case of Primaquine Phosphate's. And band at 3427 cm^{-1} is assigned to N-H stretching vibration. This is good agreement with values reported by Yutaka.

J. PO_4 Vibration

The PO_4^{3-} ion has two infrared active vibrations, a P-O stretching vibration and a O-P-O bending vibration. In a work on strontium orthophosphate crystal PO_3 symmetric and asymmetric stretching vibration have been reported to occur at 990 cm^{-1} and 1090 cm^{-1} respectively. The O-RO bending vibration being skeletal occurs around 400 cm^{-1} . In the FTIR spectrum of P.P. The P-O-asymmetric stretching is seen as a shoulder to the 988 cm^{-1} based and the asymmetric stretching is assigned to the sharp band 1058 cm^{-1} band.

Thus a satisfactory vibrational band assignment has been made on the drugs primaquine phosphate and chloroquine phosphate confirms the quality of the drugs.

IV. UV – VISIBLE SPECTRAL STUDIES ON PRIMAQUINE PHOSPHATE AND CHLOROQUINE PHOSPHATE.

UV- Visible is an excellent tool to study the quality of pharmaceutical drugs. Recently UV-vis Spectroscopy has been applied successfully to study blood sampler, injections and drugs (6-8) to investigate the quality of Primaquine Phosphate and Chloroquine Phosphate, the UV-visible spectrum of the samples were recorded in the $200-600\text{ nm}$ region. Using SL-159 UV-Visible spectrophotometer at Post graduate and Research department of physics, Pachaiyappa's College, Chennai - 30. The samples were dissolved in H_2O to get the stock solution. From this stock solution of different concentration were prepared to determine the λ_{max} of the drugs. The spectra are recorded, to study the effect of storage condition on these drugs, the drug samples were subjected to different storage condition like sunlight, (IR radiation and glance radiation. The spectra are presented in

A. Variation Of Absorbance With Increase In Drug Concentration

In the UV-Spectrum of primaquine phosphate the absorbance value corresponding to 260 nm is appreciable and increases as the concentration of the drug increases. Similarly in the UV- Visible spectrum of Chloroquine Phosphate the 245 nm band shows this trend. The absorbance of these bands are tabulated in Table 2.1. Therefore the 260 nm band is taken as the λ_{max} band for P.P and 245 nm band as λ_{max} for C.P. This to end is in agreement with Beer-Lambert Law as shown in Fig 1 and Fig 2.

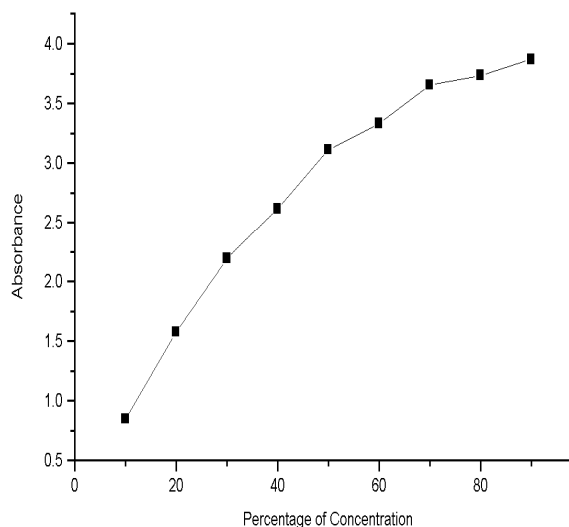


Fig 1 – Variation of Absorbance with the Concentration of Primaquine Phosphate

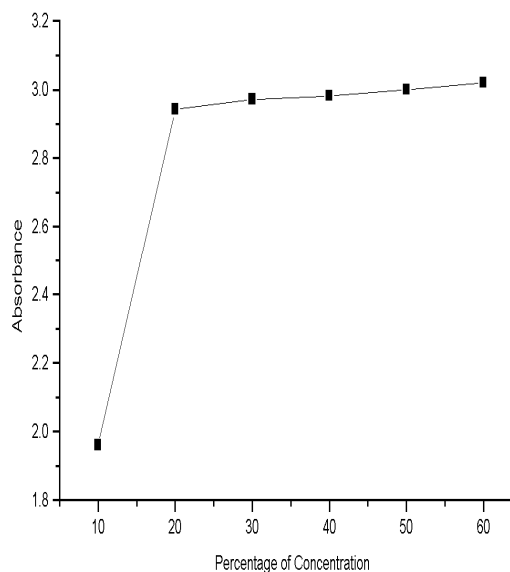


Fig 2 – Variation of Absorbance with the Concentration of Chloroquine Phosphate

V VARIATION OF ABSORBANCE OF THE DRUG UNDER DIFFERENT STORAGE CONDITIONS

The solutions of primaquine phosphate and chloroquine phosphate were subjected to different conditions. The samples were exposed to sunlight, infrared radiation and Gamma radiation separately, and the UV-spectra were recorded. The absorbance value corresponding the λ_{\max} , ie. 260 nm for primaquine phosphate and 245 nm for chloroquine phosphate under different conditions are tabulated in Table (5). Though there is no drastic change in the λ_{\max} value of the drugs, the absorbance values shows much variation under different storage condition. From table (5) it is evident that both the drug must be storied at room temp. It is also found that there is a almost shift of 10 nm in the λ_{\max} value for the drugs. When stored under Sunlight and Gamma rays and a shift of 15 nm under IR storage condition besides the variation in absorbance values.

Table 5 - Variation In λ_{\max} And Absorbance Under Different Storage Conditions

% of Concentration of Primaquine Phosphate	Absorbance (260 nm)	% of Concentration of Chloroquine Phosphate	Absorbance (245 nm)
10	0.849	10	1.960
20	1.577	20	2.943
30	2.195	30	2.972
40	2.616	40	2.982
50	3.112	50	3.000
60	3.333	60	3.020
70	3.654		
80	3.714		
90	3.868		

Storage condition	Absorbance	
	Primaquine Phosphate	Chloroquine Phosphate
Room Temp.	2.195 (260 nm)	1.960 (245 nm)
Sun Light	1.389 (259 nm)	1.478 (255 nm)
Gamma rays	1.638 (259 nm)	1.766 (255 nm)
IR	1.282 (254 nm)	1.319 (251 nm)

VI CONCLUSION

It is concluded that Primaquine Phosphate and Chloroquine Phosphate drugs were sensitive to storage conditions. Exploring them to sunlight, IR and Gamma rays alter the effectiveness of these drugs. The ideal storage condition is the room temp. The efficiency of UV-visible spectral techniques has been proved beyond doubt to and the quality of pharmaceutical days.

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