CHAPTER II

REVIEW
OXYTETRACYCLINE HYDROCHLORIDE AND CHLORTETRACYCLINE
HYDROCHLORIDE (Antibiotics)

General:

Tetracyclines are known to us for the last twenty years for their antibacterial activities. These are a family of broad spectrum antibiotics isolated from elaboration products of the Actinomycete, streptomyces rimosus, grown on suitable medium. These are complex organic molecules with a large number of functional groups possessing antibacterial activity towards a broad range of pathogenic microorganisms. The multiplicity of potential metal binding sites present in the tetracyclines has attracted much interest.

Oxytetracycline is 4-(dimethylamino)-1, 4, 4a 5, 5a, 6, 11, 12a-octahydro-3, 5, 6, 10, 12, 12a-hexahydroxy-6-methyl-1, 11-dioxo-2-naphthacenecarboxamide. Molecular formula of hydrochloride salt is $C_{22}H_{25}N_2ClO_9$. It is a yellow crystalline solid which is stable in air, soluble in water and ethanol, insoluble in chloroform and ether, decomposes at 181-182°C. The drug suppresses the growth of most gram-positive, gram-negative bacteria, spirochetes, amoebae and certain large viruses. The salt oxytetracycline hydrochloride is used for parenteral administration because of its greater solubility in water.

Chlortetracycline is 7-chloro-4-(dimethylamino)-1, 4, 4a, 5, 5a, 6, 11, 12a-octahydro-3, 6, 10, 12, 12a-pentahydroxy-6-methyl-1, 11-dioxo-2-naphthacenecarboxamide.
Its molecular formula is \( \text{C}_{22}\text{H}_{23}\text{ClN}_2\text{O}_8 \), molecular weight 478.88. The antibiotic substance is isolated from streptomycetes aureofaciens. Its hydrochloride is golden yellow crystalline solid, m.p. 168-169\(^\circ\), soluble in water (0.5-0.6 mg/ml), very much soluble in aqueous solutions above pH 8.5, fairly soluble in the cellosolves, dioxane and carbitol, slightly soluble in methanol, ethanol, butanol, acetone, ethyl acetate, benzene, practically insoluble in ether and petroleum ether.

**REVIEW OF THE RELEVANT LITERATURE ON THEIR METALLIC COMPLEXES.**

It was 1953 when Albert\(^1\) on the basis of potentiometric titrations at 20\(^\circ\)C reported the formation of 1:1 complex at lower pH and later as the pH rose during titration a 2:1 complex with \( \text{Fe}^{3+}, \text{Fe}^{2+}, \text{Cu}^{2+}, \text{Ni}^{2+}, \text{Co}^{2+}, \text{Zn}^{2+} \) and \( \text{Mn}^{2+} \). Oxford\(^2\) reported that chlortetracycline forms stable yellow complex with \( \text{Mg}^{2+}, \text{Ca}^{2+}, \text{Ni}^{2+}, \text{Cu}^{2+}, \text{Co}^{2+} \) and \( \text{Sr}^{2+} \) at higher pH (alkaline solution) soluble in n-butanol. The same author determined chlortetracycline colorimetrically by extraction of its Ca-complex into n-butanol and also proposed its use in analytical chemistry for the determination of Ca in the presence of Mg and of Co in the presence of Ni. Complexes of chlortetracycline with various metal ions were prepared by Ishidate and Sakaguchi\(^3\) using acetate buffer of pH 4.6. They reported the formation of 1:2 metal to ligand complex
with Zr (IV) and 1:1 complexes with thorium, aluminium and uranyl ions, while anhydrochlorotetracycline formed orange chelates with Zr$^{4+}$, Th$^{4+}$, Al$^{3+}$ and UO$_2^{2+}$ and spectrophotometric curves were reported for these complexes. Chlortetracycline was estimated colorimetrically as its Th(IV) complex. Sakaguchi determined chlortetracycline as its boron complex in sulphuric acid. The above method was used by Sakaguchi and Hanaki for the determination of chlortetracycline in urine. The same authors reported the formation of two complexes with boric acid, depending on the concentration of sulphuric acid, boric acid and chlortetracycline. Albert and coworkers in 1956 observed that the stability constants of a series of complexes of tetracycline, oxytetracycline and chlortetracycline with various divalent metal and trivalent metal ions are of the same order as those observed for β-diketone or α-aminoacidate complexes of these ions. On the basis of above experiments they concluded that tetracyclines must compete for metal ions in the human body. Concurrently, it was discovered that presence of excess of metal ions neutralise the effects of tetracyclines. Sakaguchi and co-workers in 1958 prepared chelates of chlortetracycline hydrochloride and oxytetracycline hydrochloride and determined their structure, solubility and stability constants. Pfizer has prepared an aqueous suspension of Mg-tetracycline complex and described its pharmaceutical importance.
Dolusio and Martin\textsuperscript{13} have described the relation of antibacterial activity of tetracycline analogs and their metal complexing properties. They reported the formation of 2:1 ligand to metal complexes of Cu\textsuperscript{2+}, Ni\textsuperscript{2+} and Zn\textsuperscript{2+} with therapeutically active tetracyclines whereas certain therapeutically inactive derivatives form only 1:1 complex with these ions. Also, using metal-free conalbumen as a model metalloenzyme drug receptor. They found binding of active tetracyclines to the receptor is greatly enhanced in the presence of Cu\textsuperscript{2+}, suggesting the existence of ternary drug-metal-receptor complexes.\textsuperscript{14} Kohn\textsuperscript{15} has shown that certain metals may mediate the binding of tetracycline to macromolecules such as deoxyribonucleic acid (DNA) and serum albumen. Shelton and Olsen have shown that the tetracycline antibiotics\textsuperscript{16} are effective by a chelating process in which they prevent the use of Mg\textsuperscript{2+}, Fe\textsuperscript{3+}, Mn\textsuperscript{2+} and other ions essential for biological synthesis by microorganisms. Taguchi\textsuperscript{17} studied mixed ligand complexes of chlortetracycline-penicillin G with Th\textsuperscript{4+}, Fe\textsuperscript{3+}, Co\textsuperscript{2+} and Cu\textsuperscript{2+} ions in acidic medium. It has been shown by paper chromatography that tetracycline, chlortetracycline, streptomycin and penicillin G effect the migration of metal ions like Cr\textsuperscript{3+}, Mn\textsuperscript{2+}, Fe\textsuperscript{3+}, Co\textsuperscript{2+}, Ni\textsuperscript{2+}, Zn\textsuperscript{2+} etc. and complexing effects of these antibiotics were also shown by electrophoresis.\textsuperscript{18} Acting on the hypothesis that tetracyclines act by uncoupling oxidative phosphorylation through inhibition of metalloflavoenzymes. Colaizzi and coworkers measured
the extent of inhibition of the metalloflavoenzyme NADH-cytochromeC-oxidoreductase by a series of therapeutically active and inactive tetracyclines. \textsuperscript{19} They presented evidence that inhibition results from chelation of iron in the enzyme by the drugs and suggested that the mode of action of tetracycline antibiotics involves inhibition of bacterial metalloflavoenzymes by chelation of enzymatically bound metal. The ultimate effect of tetracycline antibiotics in minimum doses is inhibition of bacterial protein synthesis as a result of binding of the drug to bacterial ribosomes, \textsuperscript{20-30} possibly mediated by metal ions such as magnesium \textsuperscript{20,22-25,27-30}. It has been proposed that metal ions serve to neutralize the charge on tetracyclines, thus enhancing transport through lipophilic bacterial cell walls\textsuperscript{31}. Franklin\textsuperscript{32} presented evidence that membrane penetration by tetracycline involves reversible association of the drug with membrane-associated cations, since chelating agents such as EDTA and ATP have marked inhibitory effects on uptake of tetracycline by membranes. Based on the formation of a coloured complex with Th(IV), a sensitive colorimetric method of estimation for seven tetracyclines was developed by Chatten and Krause.\textsuperscript{33} The effect of pH and time upon the stability of tetracycline complexes were also observed by above authors. Tetracycline was used as a complexing agent for the separation of uranium and thorium.\textsuperscript{34} Tetracycline complex with technitium was prepared and its use in radiopharmacy
was discussed by Breslow et al. Tetracycline was also used as a complexing agent for solvent extraction of the lanthanides and actinides. Fluorometric and photometric methods were used to study the complexes of beryllium with tetracycline in aqueous solution. The stability constants of tetracycline thorium complexes were determined.

Tetracycline and its derivatives have been known for several years for their antibacterial activity. Actual mechanism of this effect has not been definitely established; however, it appears to be linked to the ability of the molecule to form complexes with a large variety of metal ions, and therefore the behavior of tetracycline and its analogs towards metal ions have been the subject of numerous investigators. The question of which specific group the tetracycline uses to bind to the metal has not, however, been established with certainty. Conover concluded on the basis of absorption spectra that in tetracycline the binding group is the enolized \( \beta \)-diketone group at \( C_{11} \) and \( C_{12} \). Benet and Goyan have also agreed with Conover's view but they proposed that the chelating group is \( C_{10} - C_{11} \) ketophenol. On the other hand, Dolusio and Martin on the basis of potentiometric titrations of tetracycline and some of its analogs in the presence and absence of certain metal ions, have concluded that the binding group, at least for Cu(II), Ni(II), and Zn (II), is the dimethylamino at \( C_4 \) and the hydroxyl at either \( C_3 \) or
$C_{12a}$. Their conclusions were based on the assignment of the acidity constants made by Stephens\textsuperscript{49}, et.al., and recently several different groups\textsuperscript{50-52} have raised objection over these assignments. Baker and Brown\textsuperscript{53} have prepared Co and Ni complexes of three tetracyclines and studied their spectral and magnetic properties. These complexes were found to be octahedral along with two coordinated water molecules. On the basis of electronic spectra they concluded that the coordination of tetracycline molecule was through oxygen of the 1,2,3 tricarbonyl-methane system, the amide oxygen at $C_2$ and the hydroxyl at $C_1$ or $C_3$. On the basis of inhibitory properties of a series of biologically active and inactive tetracycline analogs on the metalloflavoenzyme etc., Colaizzi et.al.\textsuperscript{54}, also suggested $C_1$, $C_2$ and $C_3$ region involving the 2-carboxamide group of tetracycline as a possible site of metal binding $C_{11}$-$C_{12}\beta$-diketone has been also proposed as a possible site for chelation.\textsuperscript{55,56} Coswell and Hutchison\textsuperscript{57} have suggested another site of binding, it was multidentate combination of the $C_{11}$-$C_{12}\beta$-diketone and the $C_1$-$C_3$ tricarbonyl methane achieved through folding the molecules along $C_4$-$C_{12a}$ axis. Besides the above, sites the most important site for complexation is the $C_1$-$C_3$ tricarbonyl methane. Williams & Everett and others\textsuperscript{58,59} have made an investigation for establishing the site(s) of metal binding in tetracycline using proton NMR method. They studied the complexes of paramagnetic ions - Nd(III), Tb(III),
V(III), Cu(II), Mn(II) and Co(II) and the diamagnetic ions- La(III), Ca(II) and Mg(II) in DMSO-d₆ solution. They concluded that binding occurs at the tricarbonylmethane function of ring A, probably through oxygen donors. Narayana⁶⁰ has reported a spectrophotometric method for the determination of boron at trace levels with chlortetracycline as a new analytical reagent in concentrated, Sulphuric acid. The molar ratio of boron to chlortetracycline in the coloured complex was found to be 1:1. Thermodynamic parameters of protonated tetracycline, oxytetracycline, chlortetracycline and dimethylchlortetracycline and their complexes with In(III) were determined by Sachan et al. They proposed the binding site at C₁₀-C₁₁ ketophenol group for In(III).

A variety of techniques has been employed, but there is general disagreement as to the site of metal binding. Proposed chelating groups are (a) the C₁₀-C₁₁ ketophenol⁴⁷, (b) the C₁₁-C₁₂β-diketone,⁵⁴,⁵⁵,⁵⁶ (c) the C₄ dimethylamine and the C₃ or C₁₂α hydroxyl, (d) the C₁-C₃ tricarbonyl methane⁵₃,⁵⁴,⁵⁷,⁵₈ and (e) multidentate combination of the C₁₁-C₁₂β-diketone and the C₁-C₃ tricarbonyl methane achieved through folding the molecule along the C₄α-C₁₂α axis.⁵⁷
STREPTOMYCIN SULFATE (Antibiotics)

Streptomycin is a well known broad spectrum antibiotics. It is produced by soil Actinomycete streptomycetes griseus family Actinomycetaceae streptomycin is O-2Deoxy-2-(methylamino)-α-L-glucopyranosyl-(1→2)-O-5-deoxy-3-c-formyl-α-L-Lyxofuranosyl- (1→4)-N, N-bis (aminoiminomethyl)-D-streptamine. Molecular formula of streptomycin-A is $C_{21}H_{39}N_7O_{12}$ (molecular weight 581.58) having C- 43.37%, H-6.76%, N-16.86%, 0-33.0%. Streptomycin sulfate being more soluble in water, is used for parenteral administration and in solution for topical use. Molecular formula of streptomycin sulfate is $C_{42}H_{84}N_{14}O_{36}S_3$. It is a white crystalline hygroscopic solid and very much soluble in water. The drug is very much effective against the growth of most gram-positive bacteria, many gram-negative bacteria, spirochetes, amoebae and certain large viruses. It is a big complex organic molecule with a number of functional groups. The numerous centres for chelation present in the streptomycin molecule make metal chelation of streptomycin in solution highly probable.

REVIEW OF THE RELEVENT LITERATURE ON ITS METALLIC COMPLEXES.

Survey of literature reveals that streptomycin was reacted with a number of metal salts capable of forming chelates and several metal chelates of lower solubility in water than the drug itself have been isolated. Previously, methods of preparing stable solution of streptomycin have been described using
calcium chloride$^{63}$ and such agents as thioglycerol, thiosorbitol and thiogluco$^{64}$ but no stable insoluble preparation have been reported. Foye and Lange$^{65}$ in 1955 studied streptomycin for its complex forming properties with certain metal ions. They were able to isolate solid chelates of Cu$^{2+}$, Ni$^{2+}$ and Co$^{2+}$, and also tested the biological activity of drug complexes in guinea pigs. The copper chelates found to be relatively uncontaminated with metal hydroxide, exhibited more prolonged blood levels in guinea pigs than streptomycin but also a greater toxicity. It was also pointed out that due to the presence of a number of centres for chelation it forms stable chelates with metal ions. Raghunandan Rao$^{66}$ has shown that Iron added as FeCl$_3$$^\cdot$6H$_2$O, increased the streptomycin titre 3.6 times. .17mg Fe/100 ml of basal medium was optimal for streptomycin production by streptomyces griseus. It was observed by Gilman that traces of cobalt enhance the activity of both streptomycin and penicillin against vibrofetus.$^{67}$ Zinc complexes of streptomycin were prepared by Herbst et al. in 1957 by treating aqueous solution of streptomycin with aqueous solution of zinc salt. The complexes prepared were of low toxicity but of unchanged bacteriostatic properties and their formation was shown by electrophoresis.$^{68}$ Crosse and coworker$^{69}$ studied antifungal action of copper chelate against phytophthora infestans on tomato. Suspension of streptomycin copper-chelate (containing 13% Cu) afforded antifungal protection to tomato plant against
P. infestans in the lab. The plant gets protected approximately 6 times greater than Zineb and 50 times greater than CuOC1 and showed much greater resistance to simulated rainfall. It was observed by Kiyokazu that the practical values were lower than theoretical when Cu in formulation containing streptomycin (I), basic copper sulfate and PhHgOA was determined by thiosulfate method (Horwitz, official methods of analyses A.O.A.C. VIII ed., 1955, P.51 (C A 50 3162 C). The difference was attributed to the presence of streptomycin. Zahn and Eisenbrandt determined the chelate formation of streptomycin with some metal ions in dilute solutions. The possibility of chelate formation of streptomycin with Cu\(^{2+}\), Mn\(^{2+}\) and Mg\(^{2+}\) was studied with the aid of potentiometric titration. For comparative purposes, the corresponding experiments between di-NaEDTA (II), and oxytetracycline (III) were carried out. They reported that streptomycin(II) forms a chelate with Cu\(^{2+}\) in the alkaline medium. The streptomycin - Cu\(^{2+}\) was most probably formed in 1:1 ratio. The formation of a 1:3 was not evident as shown by Foye and Lange. With Mn\(^{2+}\) a weak chelate formation occurred in strongly alkaline medium (about pH 9.0). In 1968 Turlygina and Shpakovskaya studied the influence of CuSO\(_4\), MnSO\(_4\), FeSO\(_4\), Na\(_2\)B\(_4\)O\(_7\), streptomycin and a complex of Cu with streptomycin with cucumbers. The best effect against nodule forming nematodes was obtained with Mn and with copper streptomycin complex. Agrawal and VijayVargia have
determined the acid dissociation constant of streptomycin perchlorate and copper chelate with the help of potentiometric pH titration in aqueous solution. In the same year they were able to show the stability constant \( \log K \) and the free energy of formation \( \Delta F \) of streptomycin complexes with \( \text{Ni}^{2+} \) and \( \text{Co}^{2+} \) using conductometric and pH-metric titration techniques.\(^7^4\) It has been shown by spectrophotometric studies that streptomycin also forms 1:1 yellow coloured complex with \( \text{UO}_2^{2+} \).\(^7^5\) The apparent stability constant \( \log K \) and free energy of formation \( \Delta F \) of the complexes at 40\(^0\) are 3.37 and 8.83 \( \text{kJ} \ \text{cal/mol} \) respectively. Neibergall et al.\(^7^6\) have described a method to determine the presence of metal drug complexes in dilute solutions. Using this method streptomycin was found to complex with cupric ion and it forms only a 1:1 chelate.
PHENOBARBITONE SODIUM AND BARBITONE SODIUM
(Sedative and Hypnotic)

Phenobarbital, commonly known as luminal is a drug with hypnotic and anticonvulsive properties and has been used frequently as a treatment for epilepsy. It is soluble in organic solvents such as methanol, DMF etc. but sparingly soluble in water. Sodium salt of phenobarbital i.e. phenobarbitone sodium is sodium 5-ethyl-5-phenyl-barbiturate and is highly soluble in water. Molecular formula of phenobarbitone sodium is \( \text{C}_{12}\text{H}_{11}\text{N}_2\text{O}_3\text{Na} \) and molecular weight is 254.22. The activity mechanism of phenobarbitone sodium is well known.

Barbitone sodium is sodium-5, 5-diethyl-barbiturate. It is readily soluble in water, less soluble in alcohol and other organic solvents. pH of 0.1 molar aqueous solution is 9.4. It has been used widely as sedative and hypnotic. It is useful in insomnia, hyperthyroidism and certain psychoneurotic disorders.

REVIEW OF THE RELEVANT LITERATURE ON THEIR METALLIC COMPLEXES.

Interaction between phenobarbital and metallic ions was reported by Zwikker who obtained a compound between \( \text{Cu}^{2+} \), phenobarbital and pyridine. Earlier to Zwikker, Rising and coworkers observed that when barbitone reacts with \( \text{Cu}^{2+} \) in alcoholic medium a violet complex is formed. The formula of this violet complex was assigned as \( \text{Na}_2\text{Cu} \) (barbitone)\(_4\) on the basis of its
chemical analysis. These studies were later used for the identification of luminal and other derivatives of barbituric acid. The formation of ternary complexes has been studied by many workers who have obtained compounds such as $M(Barb)_2L_2$ and $M(Barb)L_2$, where $L$ is a base such as pyridine and imidazole etc. Bult and Klasen obtained compounds with the formula $M(Barb)_2$, $M(Barb)K$, etc. Delannoy et al. obtained a compound of $Cu^{2+}$ and barbituric acid with the formula $M(Barb)_2XH_2O$. Schubert et al. have determined the formation constant of the complexes formed by Ca and Sr with barbituric acid. Jacques attempted potentiometric and infrared spectral methods to the complexation system of biuret, sodium barbitone and analogues to study the binding of bivalent $Cu^{2+}$, $Ca^{2+}$ and $Mg^{2+}$ to the peptide linkage. Takaji et al. have proposed solution of barbital-$Cu$ complex mixed with $NH_4OH$ and ammonium alginate as a possible antidote for viper poison. The formation of $Cu(II)$ and pyridine complex with barbiturate has been discussed. Rapaport has determined barbiturates using the reaction of silver nitrate. Bjoerling et al. have determined barbituric acid derivatives as Hg-complex. Ag-complex of vernol have been prepared and analysed for metal and organic components. Perelman studied barbitone-$Na$ with $AgNO_3$ using potentiometric titrations. Complexometric determination of barbituric acid with $Cu^{2+}$, $Ag^+$, $Zn^{2+}$ etc. (total 18 metals) were carried out. Amperometric and polarographic methods have been employed to study the biuret reaction of barbitone. Sheinker
et. al. on the basis of IR spectra of barbitone complexes have concluded that the metal atom regardless of their electropositive nature were localized with the oxygen and not with the nitrogen atom. The same authors have shown the change in molecular structure of α- and γ-hydroxy derivative of N-heterocyclic compounds from the lactom and lactim series during salt formation as revealed by IR spectra. Microcrystallographic detection of certain metallic derivatives of barbituric acid has been carried out by Belova and coworkers. Barbiturate complexes with Ag in aq-NH₄OH have been reported using analysis and X-ray diffraction methods. Complexing of Cu(II) with thiobarbituric acid has been described by Toropora et al. A procedure, for the determination of barbituric acid derivatives, such as barbital, Na-barbitone etc., based on the complex formation with ZnSO₄ was described. 1:4 copper to ligand complex has been reported on the basis of colorimetric determination of Cu(II) with 2-thiobarbituric acid. Quantitative estimation of barbiturates with Cu(II) was described by Rolaski et al. Absorption and reflectance spectra of Cu(II) - thiobarbiturates complexes were studied by Morray and others. Ag(I) complexes with 5-5-disubstituted barbituric acid derivatives in aq-NH₄OH have been described. In all complexes Ag is bound through 'N'. Stability constant of the complexes of methyl nitrosobarbituric acid with bivalent ions of Cu²⁺, Co²⁺, Zn²⁺ and Fe²⁺ have been determined. Recently Jimenez et. al., have
determined stability constants of Cu(II) phenobarbituric acid in methanolic media. The stability constants were determined by potentiometric titrations and confirmed by spectrophotometric study.
AMODIAQUINE DIHYDROCHLORIDE
(Antimalarial)

Amodiquine dihydrochloride [4-[(7-chloro-4 quinolyl) amino] -α(diethyl-amino)-O-cresol, dihydrochloride, dihydrate is an antimalarial drug. It is commercially known as camoquine. The drug is a yellow solid, very much soluble in water, sparingly soluble in alcohol and slightly soluble in benzene, chloroform and ether. Molecular formula of drug is $C_{20}H_{24}Cl_{3}N_{3}O$ (molecular weight is 428.79). Solid drug decomposes at 150-160°.

REVIEW OF THE RELEVANT LITERATURE ON ITS METALLIC COMPLEXES.

An exhaustive survey of literature reveals that almost nothing has been done for the metal complexes of amodiaquine hydrochloride. A large number of work has been done with quinoline, 8- and 4-aminoquinoline and other related derivatives of quinoline ring. Hence much attention has been given in the present survey towards the complexation of behaviours of these compounds. Clarke\textsuperscript{110} reported that an aqueous solution of amodiaquine gives green precipitate when treated with cobalt thiocynate or ammonium molybdate. From the above results he concluded that, this green precipitate may be due to the formation of complexes. Reactions of gold cyanide and potassium-cadmium-iodide with amodiaquine have been studied.\textsuperscript{111} Simon has reported the formation of complexes of quinoline, isoquinoline and quinaldine with Cu(II) salts.\textsuperscript{112} Structure of some complexes of Cu-salts with
quinoline were determined by E.P.R. method. A polarographic study of Cu-8-hydroxyquinoline with a number of metallic ions were carried out. Metal complexes of 8-hydroxyquinoline have been elucidated using IR electronic spectra, molar conductance and magnetic properties. The structure of quinoline-ZnCl₂ polymer was studied by IR and by kinetic studies of polymerisation. The 2:1 complexes of 8-aminoquinoline with a number of transition metals have been carried out using UV measurements in KBr disks. Cu(II) and Zn(II) complexes of quinoline and isoquinoline have been reported by various authors and studied by using X-ray, IR, EPR, UV etc. methods. IR and UV spectra of the complexes of 8-substituted quinolines with Cu(II), Zn(II) and other metals have been reported.
CHLORPHENIRAMINE MALEATE
(Antihistaminic)

Chlorpheniramine maleate, \( \gamma \)-((4-chlorophenyl)-N,N-dimethyl-2-pyridinepropanamine, \( (Z) \). 2-butadionate (1:1) or Pyridine, 2-[P-chloro\( \alpha \)-(2-(dimethyl-amino)ethyl) benzyl] -maleate, is a white crystalline solid; melting point 130-135°C. Molecular formula of chlorpheniramine maleate is \( \text{C}_{20}\text{H}_{23}\text{Cl N}_{2}\text{O}_{4} \) (Molecular weight 390.8). It is very much soluble in water, that is, one part of chlorpheniramine maleate dissolves in 3.4 parts of water, in 10 parts of alcohol, in 10 parts of chloroform, slightly soluble in benzene, ether. It's 2% solution has got about 5 pH.

It is an antihistaminic drug. Antihistamines were able to antagonize the action of histamines. Histamine blocking activity was first detected by Bovet and Staub (1937) in a series of amines with a phenolic ether function synthesized by Fourneau.

Antihistamines are among the drugs most frequently found in medicine cabinets and all too often they are the cause of accidental poisoning in young children or the instrument of suicide in adults.

REVIEW OF RELEVANT LITERATURE ON ITS METALLIC COMPLEXES.

So far almost nothing has been reported about ligational aspect and physicochemical properties of chlorpheniramine maleate. Most of the reactions given in the literature are in connection with identification, isolation and estimation of drug. Hence along with the survey of chlorpheniramine maleate complexes, the survey
of related compounds like other antihistamines, histamines, pyridine, substituted pyridine and their derivatives were also made.

Michel and Andrews (1961)\textsuperscript{126} studied thermodynamically the complexes of histamine with Co(II), Ni(II) and Cu(II) and have shown that a stable chelate is formed in each case. It was believed that a similar study of the complexes of antihistamines with metal ion could provide valuable results and possibly aid in evaluating the importance of complex formation in the mechanism of histamine-antihistamine activity.

The thermodynamic analysis of the complexes of a series of nine commercial antihistaminic with Cu(II), Co(II), and Ni(II) was presented.\textsuperscript{127} Results of above experiment show that a stable complex is formed in each case. The free energy of formation of complexes was suggested as a possible index of effectiveness for antihistaminic activity.

Attwood D. et al.\textsuperscript{128} have studied the phenomenon of self-association of some antihistamines in aqueous solution. Complexes of substituted pyridines with transition metal halides were studied by Gill N.S. et al.\textsuperscript{129} A polarographic study to determine chlorpheniramine maleate in pharmaceuticals has been carried out.\textsuperscript{130} Infrared spectral measurements of adduct formation between VO acac\textsubscript{2} (Hacac=pentane-2, 4-dione) and a range of substituted pyridines have been
elucidated.\textsuperscript{131} Matsunaga T\textsuperscript{132} has reported antitumor agents containing pyridyl propylamine salts (Na, K or Mg salts of chlorpheniramine maleate). For Infrared assignments for bridging cobalt-halogen stretching vibrations in several coordination compounds have been reported.\textsuperscript{133} Ion exchange method for separation and spectrophotometric determination of antihistamines in pharmaceuticals was studied.\textsuperscript{134} Adsorption of chlorpheniramine maleate by montmorillonite was studied.\textsuperscript{135} The same authors have also studied chlorpheniramine maleate-montmorillonite interaction using infrared and X-ray diffraction technique.\textsuperscript{136}
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