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Structurally Modified Atropine molecule by electroanalytical method for its increased Anesthetic Potency

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ABSTRACT

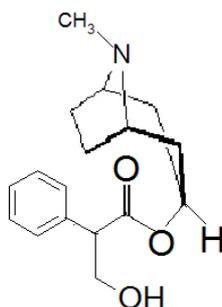
Atropine is an anesthetic drug used in anesthesia. Though the drug is being used as anesthetic but it's potency may be increased by modifying the drug by way of molecular modification, in the present study, the drug has been modified by it's complex formation with absolute methanol and conc. Sulphuric acid following standard procedure. The drug-organic compound interaction has been studied using differential pulse polarography(DPP). The results of pharmacological study indicated increased potency of modified atropine as compared to the parent drug that is atropine.

Keywords: atropine, DCP, DPP, anesthetic drug.

INTRODUCTION

Atropine is a tropane alkaloid extracted from deadly nightshade (*Atropa belladonna*), jimsonweed (*Datura stramonium*), mandrake (*Mandragora officinarum*) and other plants of the family Solanaceae. It is a competitive antagonist of muscarinic cholinergic receptors. It is absorbed from the gastro-intestinal tract, and is excreted in the urine. It is a secondary metabolite of plants and serves as a drug with a wide variety of effects. It is a competitive antagonist for the muscarinic acetylcholine receptor. It is classified as an anticholinergic drug. Being potentially deadly, it derives its name from Atropos, one of the three Fates which, according to Greek mythology, chose how a person was to die. Atropine is a *core* medicine in the World Health Organization's "Essential Drugs List", which is a list of minimum medical needs for a basic health care system. Atropine undergoes hepatic metabolism and has a plasma half-life of 2-3 hours. Atropine ampoules should be stored away from light and never be frozen.

Atropine is found in many members of the Solanaceae family. The most commonly-found sources are *Atropa belladonna*, *Datura inoxia*, *D. metel*, and *D. stramonium*. Other sources include members of the *Brugmansia* and *Hyoscyamus* genera. The *Nicotiana* genus (including the tobacco plant, *N. tabacum*) is also found in the Solanaceae family, but these plants do not contain atropine or other tropane alkaloids.



Atropine

The IUPAC name of Atropine is benzeneacetic acid, alpha-(hydroxymethyl)-8-methyl- 8-azabicyclo{3.2.1}oct-3-yl ester endo -(±), its structure is depicted above. Atropine sublimes under high vacuum at 93 to 110 °C and has a melting point of 114 to 116 °C. Atropine has low solubility in water (approximately 1g atropine in 455ml water and 1 g atropine in 90ml water at 80 °C). One gram is soluble in 2 ml alcohol, 2.5ml alcohol at 60°C, 27 ml of glycerol, 25ml ether and 1 ml chloroform. Atropine is optically inactive.

Atropine is a racemic mixture of D-hyoscyamine and L-hyoscyamine, with most of its physiological effects due to L-hyoscyamine. Its pharmacological effects are due to binding to muscarinic acetylcholine receptors. It is an antimuscarinic agent. The most common atropine compound used in medicine is atropine sulfate ($C_{17}H_{23}NO_3$)₂·H₂SO₄·H₂O, the full chemical name is 1α H, 5α H-Tropan-3-α ol (±)-tropate(ester), sulfate monohydrate.

EXPERIMENTAL SECTION

Chemicals and reagents

All the chemicals used to prepare experimental sets were of Himedia/CDH grade. Borate buffer (Borax Ranbaxy grade and NaOH BDH grade) was used. 1M stock solution was prepared by dissolving a requisite amount of the respective matter in double distilled water. The drug, under study were procured from their manufactures/market, i.e. Atropine [Himedia India Ltd.]. The stock solution of this authentic drug was prepared by the following method:

Atropine: ($C_{17}H_{23}NO_3$, White powdered compound, M.W. - 289.369)

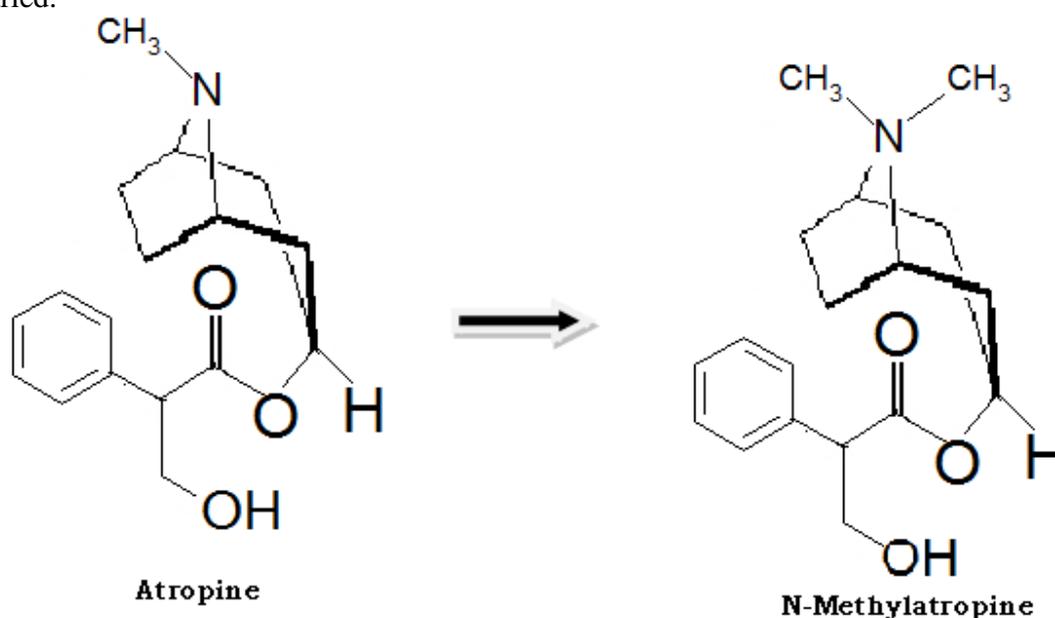
0.01M stock solution of atropine was prepared by dissolving the weighed amount of the drug in water.

Synthesis and analysis of n-methyl atropine:-

Atropine molecule was modified following the procedure discussed to below 4.0 gm of atropine was taken in a round bottom flask. 10ml absolute methanol and 1ml conc. Sulphuric acid was

added to it. A few small chips of porous porcelain were also placed in the flask. The flask was attached a reflux condenser. The mixture was gently boiled for 4 hours.

Then the excess of alcohol was distilled off on a water bath and the contents were allowed to cool. The residue so obtained was poured a mixture of 250ml of water and 100ml carbontetrachloride contained in a separatory funnel. The contents of the funnel were shaken gently for 10 min. and allowed to stand for 2 min. Lower CCl₄ layer carefully collected in a flask and the upper aqueous layer was rejected. The CCl₄ layer was washed once with water, and dried by pouring in to a small dry conical flask containing about 1gm magnesium sulphate. The flask was stoppered, shaken for about 5 minutes and allowed to stand for at least half an hour with occasional shaking. White crystals of N-methylatropine were obtained, which were separated and dried.



Preparation of analyte and recording of the Polarogram

0.01mg/1ml solution of atropine was prepared in water. The authentic sample solution of atropine was dissolved in water. Experimental set was prepared by taking 1ml of sample solution and (1M borate buffer)10ml of borate buffer as supporting electrolyte in a polarographic cell and the total volume was made is 50ml with distilled water. The pH of the test solution was adjusted to 8.2±0.1.

Pharmacological study

Local action of a large number of drugs in an eye can be achieved without systemic effect by the application of drugs as eye drops, or eye ointments. Most of these drugs belong to antimicrobial, autonomic or local anesthetic groups. The eye is supplied both by sympathetic and parasympathetic nerves. The superior palpebral muscle and the dilator pupillae (circular fibers) of the iris has parasympathetic supply which exercises dominant control. The ciliary muscle is also supplied by the parasympathetic nerves and when it contracts, the ciliary body is moved inwards and forwards. Because of this the lens bulges forward and the eye is accommodated for near vision. The opposite effect is produced by the relaxation of ciliary

muscle resulting in paralysis of accommodation (cycloplegia). When the pupil dilates, the iris folds back near the opening of the canal of schlemm and the drainage of aqueous humour is decreased thereby increasing in intraocular pressure. Constriction of the pupil, by opposite action, will increase drainage and reduce intraocular pressure ⁽⁴²⁾.

Topically applied drugs can affect the eye by changing conjunctival congestion, papillary size can be measured by placing a transparent plastic scale in front of the eye but as close as possible. Light reflex is elicited by directing the light of a torch towards the pupil. The sensitivity of the cornea is tested by gently touching the cornea with a fine cotton swab stick from the side and not from the front of the eye. This elicits corneal reflex which manifests as blinking of the eyelids.

RESULTS AND DISCUSSION

The direct current polarogram (DCP) and differential pulse polarogram (DPP) of the authentic sample solution of atropine in Borate buffer (1M) at pH 8.2±0.1 produced one well-defined polarographic wave/peak with $E_{1/2}/E_p = -1.52V$ vs SCE.

To ascertain as to whether the wave/peak is due to atropine present in the solution, a known quantity of standard solution of atropine was added to the analyte and polarogram was recorded under above experimental conditions, An increase in wave height of the polarogram due to atropine was observed without any change in half wave/peak potential, thus confirming the presence of atropine in the solution.

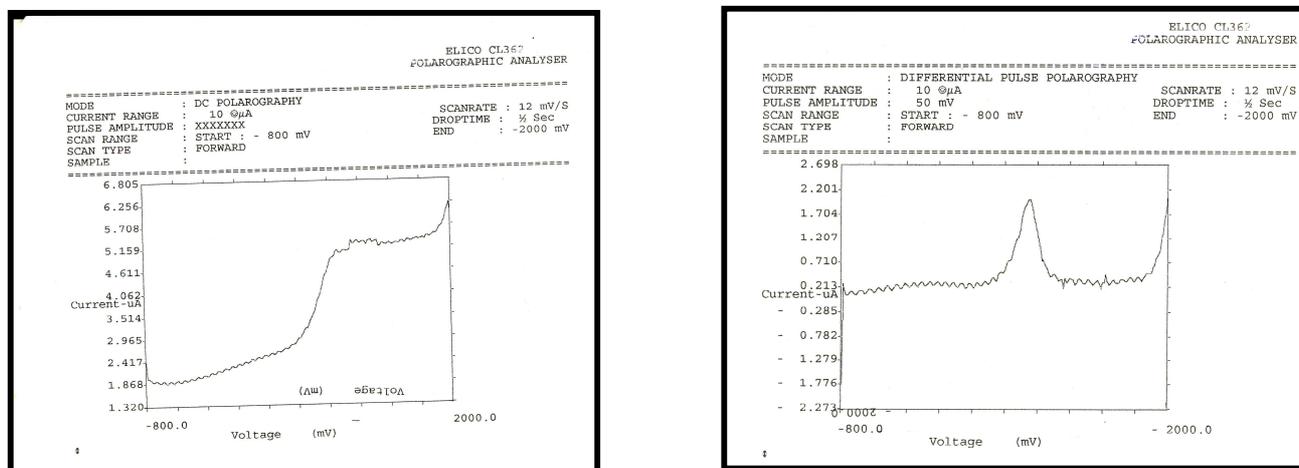


Fig 1.1 (a) Direct current Polarogram and Differential pulse Polarogram of (0.001M) atropine in borate buffer (0.1M) at pH 8.2±0.1.

On recording the polarogram of atropine in (1M) borate buffer at pH 8.2±0.1. It produced a well defined polarographic wave with $E_{1/2} = -1.52V$ vs. SCE. And when the modified atropine that is n-methyl atropine was polarographically analyzed in similar experimental condition the resulting polarogram was given also very well defined wave. The shift in half wave potential i.e. from -1.52V to -1.56V indicated the formation of n-methyl atropine. The polarographic analysis of

varying concentration of n-methyl atropine under the above set experimental conditions shown linear relationship between i_d and aryl n-methyl atropine concentration. Thus enabling its quantitative and qualitative analysis.

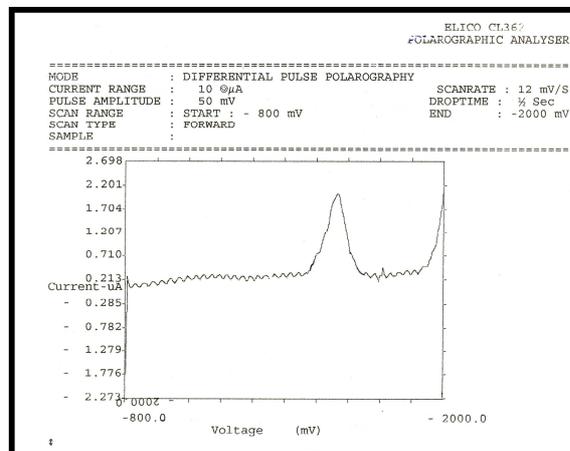
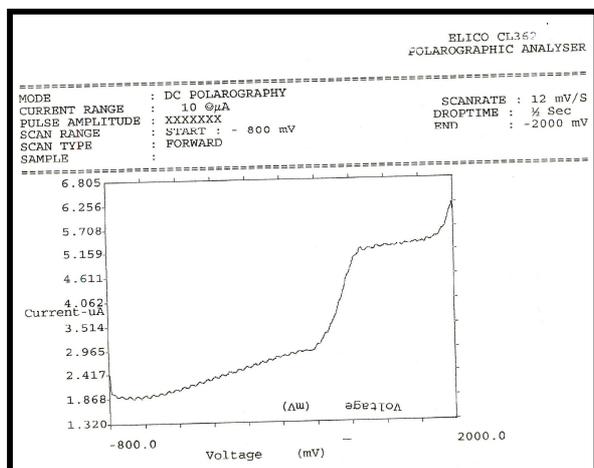


Fig 1.2 Direct current polarogram and Differential pulse polarogram of (0.001M) modified atropine (N-methylatropine) in Borate buffer (0.1M) at pH 8.2±0.1.

IR characterization of the test samples.

The IUPAC name of Atropine is benzeneacetic acid, alpha-(hydroxymethyl)-8-methyl- 8-azabicyclo{3.2.1}oct-3-yl ester. The observed results were also supplemented by the FTIR study on the drug and its modified form. FTIR spectra of authentic atropine (Fig. 3-1.3) clearly shows characteristics signals at 1111cm^{-1} (C-N), 3080cm^{-1} (aromatic ring), 3225cm^{-1} (OH), 2964cm^{-1} (methyl group). And the other hand modified drug (n-methylatropine) (Fig.3-1.4) has given characteristics signals at 1109cm^{-1} (C-N), 3082cm^{-1} (aromatic ring), 3223cm^{-1} (OH), 2997cm^{-1} (methyl group) and another methyl group given 2850cm^{-1} . Thus confirming the presence of methyl group in modified form.

Table

S. No.	Time interval in (minutes)	Control	Standard drug Atropine	Modified drug n-methylatropine
1.	Initial	.7cm	.7cm	.7cm
2.	After 10 minutes	.7cm	.8cm	.9cm
3.	20 minutes	.7cm	.9cm	1.2cm
4.	30 minutes	.7cm	1.3cm	1.8cm
5.	40 minutes	.7cm	1.0cm	2.0cm
6.	50 minutes	.7cm	.9cm	1.5cm
7.	60 minutes	.7cm	.8cm	1.2cm
8.	70 minutes	.7cm	.7cm	.9cm
9.	80 minutes	.7cm	.7cm	.8cm
10.	90 minutes	.7cm	.7cm	.7cm

Pharmacological Experiments

A rabbit was placed in a Rabbit holder (box) keeping the head out side. The size of the rabbit pupil of both eyes was observed. The effect of light reflex of the rabbit's eye to and fro. The corneal reflex was examined by touching a side of the cornea with a cotton piece. A few drops of

atropine were instilled in the conjunctiva (4-6 times) over a period of 8-10 minutes in the right eye of the rabbit. The left eye of the rabbit served as control. In which normal saline of instilled. The pupillary size was recorded after 10 minutes of drug instillation and the data was tabulated. The experiment was repeated with modified atropine molecule.

CONCLUSION

On the basis of reported data and ongoing discussion it could be concluded that the proposed electroanalytical methods provide accurate and precise data on trace analysis of atropine and its modified forms. The techniques are best suited because of simplicity as well as economics of the procedure for the simultaneous qualitative and quantitative determination of traces of active principles of drugs and may be recommended for their possible use in medicinal industries. The author also recommends the modified drugs to the therapeutic experts to ascertain the possible use of these modified forms as more potent anesthetics in lieu of parent atropine drug. The observed analytical data clearly speaks the formation of modified form of the drug (atropine) in 1:1 ratio in each case.

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