State of the Art and Scope of the Investigation
2.1. SELECTION OF DRUGS

Electroanalysis of organic substances belonging to drugs containing various basic electroactive units have been the subject of interest for many electroorganic chemists and electroanalysts. Perusal of literature revealed that little work has so far been carried out in the electrochemical aspects of the drugs such as Pheniramine, Acetylsalicylic acid, Acetaminophen and Dipyrone on modified electrodes. This led to the selection of these drugs for the present investigation. The study of electrochemical behaviour of these drugs also led to analytical applications. Hence the main objective of the present investigation is to study the electrochemical behaviour of selected drugs on modified electrodes using voltammetry and the development of development of electroanalytical method for the determination of these drugs. The table 2.1 presents the structure of the four drugs selected for the present investigation.

Table 2.1
Drugs selected for the present investigation

<table>
<thead>
<tr>
<th>S. No.</th>
<th>Compound</th>
<th>Structure</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Pheniramine (PA)</td>
<td><img src="image" alt="" /></td>
</tr>
<tr>
<td>2</td>
<td>Acetylsalicylic acid (ASA)</td>
<td><img src="image" alt="" /></td>
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</table>
2.2. PHENIRAMINE

Pheniramine is an antihistamine drug. An antihistamine is a drug which serves to reduce or eliminate effects mediated by histamine, an endogenous chemical mediator released during allergic reactions, through action at the histamine receptor. In common use, the term antihistamine refers only to $H_1$-receptor antagonists, also known as $H_1$-antihistamines [201].

Histamine, acting on $H_1$-receptors, produces pruritis, vasodilatation, hypotension, flushing, headache, tachycardia, bronchoconstriction, increases vascular permeability, potentiates pain, and more [202]. $H_1$-antihistamines are clinically used in the treatment of histamine-mediated allergic conditions. Specifically, these indications may include: [203]

Antihistamines can be administered topically (through the skin, nose, or eyes) or systemically, based on the nature of the allergic condition. Pheniramine is used to treat allergic conditions such as hay fever or urticaria. It is generally sold in combination with other medications, rather than as a stand-alone drug. Pheniramine block the effects of the naturally occurring chemical histamine in the body prevent sneezing; itchy, watery eyes
and nose; and other symptoms of allergies and hay fever. Pheniramine is used to treat nasal congestion and sinusitis (inflammation of the sinuses) associated with allergies, hay fever, and the common cold.

The patient may not be able to take pheniramine or may require a dosage adjustment or special monitoring during treatment if the patient has any of the conditions listed above. Pheniramine is in the FDA pregnancy category B. This means that it is unlikely to harm an unborn baby. Pregnant ladies are generally warned about pheniramine. Pheniramine passes into breast milk and may harm a nursing infant.

If the patient is over 65 years of age, he may be more likely to experience side effects from pheniramine. He may require a lower dose of this medication. Children are more susceptible than adults to the effects of medicines and may have unusual reactions. An overdose can cause serious harm. Symptoms of a pheniramine overdose include a dry mouth, large pupils, flushing, nausea, and vomiting. One has to use caution when driving, operating machinery, or performing other hazardous activities. Pheniramine may cause dizziness or drowsiness. If one experience dizziness or drowsiness, he should avoid these activities. Alcohol may increase drowsiness and dizziness while taking pheniramine.

Pheniramine may increase the effects of other drugs that cause drowsiness, including antidepressants, alcohol, other antihistamines, pain relievers, anxiety medicines, seizure medicines, and muscle relaxants. Dangerous sedation, dizziness, or drowsiness may occur if pheniramine is taken with any of these medications.

2. 3. ACETYLESALICYLIC ACID

Acetylsalicylic acid (ASA) or Aspirin is a drug in the family of salicylates, often used as an analgesic (against minor pains and aches), antipyretic (against fever), and
anti-inflammatory. It has also an anticoagulant ("blood-thinning") effect and is used in long-term low-doses to prevent heart attacks. Acetylsalicylic acid is one of the oldest medicines that yet plays an important role in the modern therapeutics. The main metabolite of the acetylsalicylic acid is the salicylic acid that results from its hydrolysis and can be qualitatively determined giving indirectly the quantity of the former.

Aspirin was the first discovered member of the class of drugs known as non-steroidal anti-inflammatory drugs (NSAIDs), not all of which are salicylates, though they all have similar effects and a similar action mechanism. Hippocrates, a Greek physician, wrote in the 5th century BC about a bitter powder extracted from willow bark that could ease aches and pains and reduce fevers. This remedy is also mentioned in texts from ancient Sumeria, Egypt and Assyria. Native Americans claim to have used it for headaches, fever, sore muscles, rheumatism, and chills. The Reverend Edward Stone, a vicar from Chipping Norton, Oxfordshire England, noted in 1763 that the bark of the willow was effective in reducing a fever [204].

Aspirin should be avoided by those known to be allergic to aspirin, ibuprofen or naproxen. It is generally recommended that one seek medical help if symptoms do not improve after a few days of therapy. Caution should be taken in patients with kidney disease, peptic ulcers, mild diabetes, gout or gastritis; manufacturers recommend talking to one's doctor before using this medicine. Taking aspirin with alcohol increases the chance of stomach bleeding. Children, including teenagers, are discouraged from using aspirin in cold or flu symptoms as this has been linked with Reye's syndrome. Patients with hemophilia or other bleeding tendencies should not take salicylates. Some sources recommend that patients with hyperthyroidism avoid aspirin because it elevates T4 levels.

Long-term treatment with high doses (arthritis and rheumatic fever): often increased liver enzymes without symptoms, rarely reversible liver damage. The
potentially fatal Reye's syndrome may occur, if given to pediatric patients with fever and other signs of infections. The syndrome is due to fatty degeneration of liver cells. Up to 30 percent of those afflicted will eventually die. Prompt hospital treatment may be life-saving.

Actetylsalicylic acid overdose has serious consequences and is potentially lethal. Possible effects of overdose include tinnitus, abdominal pain, hypokalemia, hypoglycemia, pyrexia, hyperventilation, dysrhythmia, hypotension, hallucination, renal failure, confusion, seizure, coma and death.

If the overdose was intentional, the patient should undergo psychiatric evaluation, as with any suicide attempt. Fifty-two deaths involving single-ingredient aspirin were reported in the United States in the year 2000 [204].

The consumption of acetylsalicylic acid is always increasing and corresponds to several tons per year. For instance, in 1997 it was claimed that it could to be as high as 20 000 tons only in the United States [205].

The determination of acetylsalicylic acid in pharmaceutical preparations is important for assessment of their quality and, in blood serum, to control therapies based on this compound and for toxicological procedures. Intoxication accidents with children, for instance, are not rare due to the accessibility of this drug [206].

2.3. ACETAMINOPHEN

Acetaminophen (AAP) or paracetamol is well established as a leading non-prescription antipyretic analgesic drug and it belongs to analgesic drug. An analgesic (colloquially known as a painkiller) is any member of the diverse group of drugs used to relieve pain and to achieve analgesia. This derives from Greek an-, "without", and -algia, "pain". Analgesic drugs act in various ways on the peripheral and central nervous system; they include acetaminophen, the nonsteroidal anti-inflammatory drugs
(NSAIDs) such as the salicylates, narcotic drugs such as morphine, synthetic drugs with narcotic properties such as tramadol, and various others. Some other classes of drugs not normally considered analgesics are used to treat neuropathic pain syndromes; these include tricyclic antidepressants and anticonvulsants.

Analgesics are frequently used in combination, such as the acetaminophen and codeine preparations found in many non-prescription pain relievers. They can also be found in combination with vasoconstrictor drugs such as pseudoephedrine for sinus-related preparations, or with antihistamine drugs for allergy sufferers.

It is remarkably safe in recommended doses, but because of its wide availability, deliberate or accidental overdoses are fairly common. Acetaminophen, unlike other common analgesics such as aspirin and ibuprofen, has no anti-inflammatory properties, and so it is not a member of the class of drugs known as non-steroidal anti-inflammatory drugs (NSAIDs). In recommended doses, acetaminophen does not irritate the lining of the stomach, affect blood coagulation, or function of the kidneys.

Acetaminophen is safe in pregnancy, and does not affect the closure of the fetal ductus arteriosus (as NSAIDs can). Unlike aspirin, it is safe in children as acetaminophen is not associated with a risk of Reye's syndrome in children with viral illnesses.

Acetaminophen has a narrow therapeutic index – the therapeutic dose is close to the toxic dose. Additionally, acetaminophen is contained in many preparations (both over-the-counter and prescription only medications). This means that, despite being one of the safest analgesics available at recommended doses, there is a large potential for overdose and toxicity [207].
The toxic dose of acetaminophen is highly variable. In adults, single doses above 10 grams or 150 mg/kg have a reasonable likelihood of causing toxicity [208]. Toxicity can also occur when multiple smaller doses within 24 hours exceed these levels, or even with chronic ingestion of doses as low as 4 g/day, and death with as little as 6 g/day. In children, acute doses above 200 mg/kg could potentially cause toxicity. This higher threshold is largely due to children having relatively larger kidneys and livers than adults and hence being more tolerant of acetaminophen overdose than adults [209].

Chronic excessive ethanol (alcohol) consumption can induce CYP2E1, thus increasing the potential toxicity of acetaminophen [210]. For this reason, other analgesics such as aspirin or ibuprofen are sometimes recommended for hangovers. Fasting is a risk factor, possibly because of depletion of hepatic glutathione reserves.

Acetaminophen is extremely toxic to dogs and cats, and should not be given to them under any circumstances. Cats lack the necessary enzymes to safely break acetaminophen down and tiny fractions of a normal tablet for humans may prove fatal [211]. Any cases of suspected ingestion should be taken to a veterinarian immediately for detoxification [212].

2.4. DIPYRONE

Dipyrone (DP) or Metamizole sodium ([2,3-dihydro-1,5-dimethyl-3-oxo-2-phenyl-1H-pyrazol-4-yl] methylamino)methanesulfonate) is a non-steroidal anti-inflammatory drug (NSAID), commonly used in the past as a powerful painkiller and fever reducer. It is better known under the names Dipyrone, Analgin, and Novalgin.
The German company Hoechst AG first synthesized dipyrone in 1920, and its mass production started in 1922. It remained freely available worldwide until the 1970s, when it was discovered that the drug carries a small risk of causing agranulocytosis - a very dangerous and potentially fatal condition.

In other words, one should expect 50 to 500 deaths annually due to metamizole in a country of 300 million, assuming that every citizen takes the drug once a month. This is not a very high rate, especially compared to other drugs - for example, the prescription drug clozapine is known to be at least 50 times more likely to trigger agranulocytosis. However, at the time the risk was assumed to be much greater [213] and, as such, excessive for an over-the-counter analgesic, especially considering the existence of safer alternatives (aspirin, acetaminophen, and ibuprofen).

Dipyrone was banned in Sweden in 1974, in the United States in 1977; more than 30 countries, including Japan, Australia, and most of the European Union, have followed suit. In these countries, metamizole is still occasionally used as a veterinary drug. Some pharmaceutical companies, notably Hoechst and Merck, continue to develop metamizole-containing drugs and market them in some countries. In Germany it became a prescription drug, sold under the brands Novalgin, Analgin, Berlosin, Metalgin, Metamizol-Puren, Novaminsulfon.

In the rest of the world (esp. in Mexico, India, Brazil, Russia, Third World countries) dipyrone is still freely available over-the-counter and remains one of the most popular analgesics.

Dipyrone received brief period of attention by American media in 2001 [214], when a Latino immigrant boy was admitted into a Salt Lake City clinic with symptoms of agranulocytosis.
2.5. SCOPE OF THE INVESTIGATION

2.5.1. Electrochemical Studies

Cyclic voltammetry is often used as a first electrochemical technique to study the electrochemical reactions. It is an important technique because of its ability to generate potentially reactive species which enables us to examine them immediately by reversal. Its experimental simplicity leads to its ready usage and a variety of systems are extensively studied. Electroorganic chemists have used this technique for the following purposes.

- To characterise the surface and interfacial structures
- To evaluate the electron transfer reactions
- To determine reaction mechanisms and substituents effects
- To compare electrochemical reaction system with bio-systems and
- To evaluate the effects on the redox potential of the central metal ion in complexes and multi nuclear clusters.

The usefulness and importance of this technique has led to the selection of cyclic voltammetry for this investigation. To substantiate and supplement cyclic voltammetric results other electrochemical methods such as chronocoulometry (CC) and controlled potential coulometry (CPC) have been chosen for this investigation. Now a days, coated electrode systems / modified electrode systems are very much employed to characterise organic compounds. Hence riboflavin modified glassy carbon electrode (RB/GCE), conducting polymer modified glassy carbon electrode such as polypyrrole (PPy/GCE), polyethylenedioxythiophene, deposited glassy carbon electrode (PEDOT/GCE) and sodium montmorillonite clay modified glassy carbon electrode (NaMM/GCE) are utilised here to study electrochemical behaviour of the selected drugs.
The main objectives of voltammetric studies of the selected four drugs are as follows:

➢ To study the electrochemical behaviour of selected drugs

➢ To study the effect of pH on the reduction/oxidation of the drugs

➢ To find out the diffusion coefficients through chronocoulometry

➢ To determine the number of electrons transferred from controlled potential coulometry

➢ To investigate possible redox mechanisms

➢ To find out the electrochemical behaviour in modified electrode systems

➢ To find out the suitable electrode system for electroanalytical determination and

➢ Optimisation of stripping voltammetric procedure by differential pulse and square wave.