Hippocrates stated ‘Healing is a matter of time, but it is sometime also a matter of opportunity’ and this opportunity has been served to all the lives in the form of life saving drugs. The drugs play the crucial role to survive the world. Among innumerable number of drugs, the historical development, syntheses, metabolism, effects and side effects of two very frequently used drugs, paracetamol and aspirin, has been reported.

**Key words**: Paracetamol, Aspirin, Metabolic path, Treatment, Toxicity

1. **INTRODUCTION**

Chemistry is one of the most fascinating subjects because of its presence in every nook and corner around the world. During our journey form gorgeous diamond (Harkins, 1942) to the ingredients of a special spicy (Glassford, 1928) dish or from water (Whipple, 1914) to life-saving drugs (Cutting, 1946) wherever we go we find chemistry. Chemistry has been playing very important role for the service of mankind from its very inception (Charles, 1976). Among all such things the discovery and developments of many life-saving drugs added a new direction in the advancement of civilization. The drugs are meant by some chemical substances which are used for treatments of various diseases and are responsible for reducing the sufferings. There are so many drugs for such treatments among which ‘paracetamol’
2. WHAT ARE PARACETAMOL AND ASPIRIN?

Paracetamol is an organic compound called 4-hydroxy acetanilide or 4-acetamidophenol or N-acetyl-p-aminophenol and is a very common analgesic and antipyretic medicine that is used for the relief of fever, headaches and other minor pains. In the US Pharmacopoeia, it is known as acetamidophen (Figure 1). Aspirin is called acetylsalicylic acid or 2-(acetyloxy) benzoic acid or salicylic acid acetate and is a very common non-steroidal anti-inflammatory drug (NSAID). It is taken orally (Figure 2).

3. PHYSICAL PROPERTIES

Paracetamol is white in colour, odourless crystalline powder having a bitter taste. Its melting point is 169 °C. It is soluble in water (1.4 g/100 ml) and in common organic solvents like alcohol, acetone, glycerol, propylene glycol, chloroform etc. but insoluble in benzene and ether. It is also soluble in solutions of alkali hydroxides. The pH of the saturated aqueous solution is about 6 and is stable, but the stability decreases in presence of acid or alkali as it is slowly hydrolyzed into p-aminophenol and acetic acid. Aspirin is also a white crystalline powder with a melting point of 135 °C and is a weak organic acid with pKa 3.5. It is very much soluble in water as well as in common organic solvents like alcohol, chloroform and ether. Though aspirin is a stable compound it decomposes by boiling water or when dissolved in solutions of alkali hydroxides and carbonates.

4. HISTORICAL BACKGROUND

From the historical records, it is known that the father of modern medicine, Hippocrates (460 - 377 B.C.) was said to recommend a brew made with leaves from willow tree to ease pain of certain eye diseases and child birth. Salicin, the chemical compound found in white willow bark was isolated and named by Johann Buchner, Professor of Pharmacy at the University of Munich, in 1928. The extraction procedure of Salicin was later improved by French chemist Henri Leroux and he extracted salicin in crystalline form for the first time. So in ancient and medieval times, salicins and quinines were commonly prescribed as antipyretic medicines. Quinines are chemical compounds found in cinchona bark. But in around 1880s, cinchona tree became scarce and that is why its bark became short in supply and the scientists started to search for the alternatives. Two alternatives antipyretics were developed in 1880s which included acetanilide in 1886 and phenacetin in 1887. Both of them had the advantage over quinine having both antipyretic and analgesic actions.

Though in 1878, Harmon Northrop Morse first synthesized paracetamol by reducing p-nitrophenol with tin in glacial acetic acid, it was not used medically till 1893 i.e. 15 years after its birth. In 1893, a compound now known as paracetamol having analgesic and antipyretic properties was found in urine extract of people’s who had taken phenacetin and surprisingly in 1899 the same compound was found to be a urinary metabolite of acetanilide. But, such interesting observations were largely ignored at that time.

However, almost after 50 years, in 1948 Bernerd Brodie and Julius Axelrod were succeeded in assigning paracetamol as a metabolite of both phenacetin and acetanilide. Their work led to believe that the rapid conversion of both acetanilide and phenacetin to paracetamol was responsible for their clinical actions within the body. This was again supported by the fact that the level of analgesic and antipyretic effects of paracetamol were in the same order as those of its parent components.

In 1955, paracetamol went on sale in the United States under the brand name 'Tylenol'. Thereafter in 1956, 500 mg tablets of paracetamol went on sale in the United Kingdom under the trade name 'Panadol', primarily as prescription product. In June 1958 'Panadol Elixir' was formulated exclusively for the children. In 1963, paracetamol was added to British Pharmacopoeia and it has gained its popularity as an over-the-counter (OTC) drug.

To know the development of aspirin we should look back in 1850s and later. French scientist Charles Frederic Gerhardt in 1853 first prepared acetyl salicylic acid by treating neutralized salicylic acid by buffering it with sodium (sodium salicylate) with acetyl chloride. Later, in 1897, Felix Hofmann of Bayer Company in Germany also prepared...
The mechanistic pathway of paracetamol was thought to be similar to that of ‘aspirin’ for a long time due to their quite similar structural skeleton. The mechanistic route of aspirin and other non-steroidal anti-inflammatory drugs (NSAIDs) was known to proceed by blocking the cyclooxygenase enzymes (known as COX-1 and COX-2) and thereby inhibiting the production of prostaglandin (Collier, 1971) which is responsible for inflammatory response to injury (Vane, 1971). Actually cyclooxygenase (COX) plays crucial role for the conversion of phospholipids to prostaglandins and thromboxanes which are responsible for an increased blood flow and associated effects during inflammation i.e. swelling and pain in the local affected area. Such actions of NSAIDs in blocking COX-1 were also known to be associated with the unwanted gastrointestinal side effects, i.e. NSAIDs have detrimental effects on stomach lining, where prostaglandin serves a protective role. Actually, these isoenzymes (COX-1 and COX-2) catalyze the conversion of arachidonic acid to prostaglandinH$_2$ (PGH$_2$) which is the immediate precursor to PGF$_2\alpha$, PGF$_{2\alpha}$, PGF$_2\alpha$ and thromboxane (TX)A$_2$. The irreversible inhibition produced by aspirin (as compared to most non-steroidal anti-inflammatory drug (NSAIDs) which are reversible inhibitors) requires generation of new enzyme to restore function, which can only be achieved in nucleated cells. The peripheral inhibition of COX-2 formation at the site of tissue injury, and centrally within the CNS is responsible for the analgesic activity of Aspirin. Its antipyretic effects are also central. Aspirin exerts cardiovascular effects in the platelet and in the vessel wall.

Aspirin is metabolized (Scheme 4) by deacylation to salicylic acid, which is also active, acting as a reversible inhibitor of the enzyme. Salicylic acid is then metabolized primarily to two major inactive metabolites: salicyluric acid arises from conjugation of salicylic acid with glycine, and gentisic acid arises from p-hydroxylation mediated by acetylsalicylic acid by derivatizing one of the hydroxyl functional groups in salicylic acid with an acetyl group and he named the new medicine aspirin (‘a’ for acetyl – the systematic name for the compound at the time was acetylsalicylic acid, ‘spir’ for spirea, the meadow sweet plant). Bayer patented aspirin in 1900. After 1915 aspirin became commercially available as tablets in the markets. The use of aspirin in the reduction of heart attack was first noticed in 1948 by Dr. Lawrence Craven, a California general practitioner. Thereafter, several significant research works on the clinical usages of aspirin were carried out. In 1990s more than 10 million kilograms of aspirin were made in the US each year. Nowadays aspirin is not only used as a pain-killer but has also been proposed as effective in reducing the incidence of heart disease.

**5. SYNTHESES OF THE DRUGS**

Starting from phenol, paracetamol can be synthesized as follows:

a) Step-I: Nitration of phenol by using sulphuric acid and sodium nitrate

b) Step-II: The para isomer is separated from ortho isomer by fractional (steam) distillation.

c) Step-III: The p-nitrophenol is reduced to its amino analogue using sodium borohydride in basic medium.

d) Step-IV: The p-aminophenol is reacted with acetic anhydride to give paracetamol.

This can be shown schematically in Scheme 1.

Hoechst-Celanese introduced another simpler approach for the synthesis of paracetamol by acylation of phenol with acetic anhydride catalyzed by HF; thereby conversion of the ketone to ketoxime on reaction with hydroxylamine, followed by acid catalyzed Beckmann rearrangement to give the desired drug (Scheme 2).

Aspirin is also synthesized starting from phenol as follows:

Step I: This is the Kolbe-Schmitt carboxylation reaction, in which sodium phenoxide adds to carbon dioxide gas under pressure to generate sodium salicylate which on acidification affords salicylic acid.

Step II: It is a nucleophilic acyl substitution reaction. Salicylic acid is acetylated with acetic anhydride in the presence of sodium hydroxide.

The schematic representation of the above two steps are given in Scheme 3.

**6. STRUCTURE AND REACTIVITY**

Paracetamol consists of 1,4- disubstituted benzene ring by a hydroxyl group and nitrogen atom of acetamide group respectively. The system is highly conjugated as all the lone pairs and the π-electrons are all in conjugation with each other. This conjugation increases the acidity of hydroxyl group, while decreases the basicity of oxygen and nitrogen. There is an active acidic group in aspirin and it may react with water or nucleophiles (e.g. amines and hydroxy groups). It may also react with acetanilide, amidopyrine, phenazone, hexamine, iron salts, phenobarbitone sodium, quinine salts, potassium and sodium iodides, alkali hydroxides, carbonates, stearates and paracetanol.

**7. MODE OF ACTIONS**

The mechanistic pathway of paracetamol was thought to be similar to that of ‘aspirin’ for a long time due to their quite similar structural skeleton. The mechanistic route of aspirin and other non-steroidal anti-inflammatory drugs (NSAIDs) was known to proceed by blocking the cyclooxygenase enzymes (known as COX-1 and COX-2) and thereby inhibiting the production of prostaglandin (Collier, 1971) which is responsible for inflammatory response to injury (Vane, 1971). Actually cyclooxygenase (COX) plays crucial role for the conversion of phospholipids to prostaglandins and thromboxanes which are responsible for an increased blood flow and associated effects during inflammation i.e. swelling and pain in the local affected area. Such actions of NSAIDs in blocking COX-1 were also known to be associated with the unwanted gastrointestinal side effects, i.e. NSAIDs have detrimental effects on stomach lining, where prostaglandin serves a protective role. Actually, these isoenzymes (COX-1 and COX-2) catalyze the conversion of arachidonic acid to prostaglandinH$_2$ (PGH$_2$) which is the immediate precursor to PGF$_2\alpha$, PGF$_{2\alpha}$, PGF$_2\alpha$ and thromboxane (TX)A$_2$. The irreversible inhibition produced by aspirin (as compared to most non-steroidal anti-inflammatory drug (NSAIDs) which are reversible inhibitors) requires generation of new enzyme to restore function, which can only be achieved in nucleated cells. The peripheral inhibition of COX-2 formation at the site of tissue injury, and centrally within the CNS is responsible for the analgesic activity of Aspirin. Its antipyretic effects are also central. Aspirin exerts cardiovascular effects in the platelet and in the vessel wall.
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Scheme 4

Scheme 5
Schematic Presentation of Safe Mode Pathways
cytochrome P450. These two metabolites are then excreted in the urine. The excretion of salicylate occurs with first-order kinetics with a half-life between 2 and 19 hours, depending on the dose of aspirin administered. However, paracetamol has no such effects in recommended doses and no significant action on COX-1 and COX-2. This also excluded paracetamol from NSAIDs group. Moreover, paracetamol indirectly blocks COX, while NSAIDs block the COX directly. In 1972 it was suggested (Flower and Vane, 1972) that antipyretic action of paracetamol was mainly due to its action in brain and its non anti-inflammatory behaviour was consistent with a lack of prostaglandin inhibition by directly blocking the COX. After 30 years, in 2002 (Warner and Mitchell, 2002; Chandrasekharan et al., 2002) the
presence of a new cyclooxygenase enzyme (COX-3) was found in brain and spinal cord and this COX-3 is distinct from previously known two enzymes COX-1 and COX-2. He also suggested that paracetamol functions by inhibiting the enzyme COX-3 selectively in brain and spinal cord.

8. METABOLISM PROCESS AND TOXICITY OF PARACETAMOL

a) Safe Mode Metabolism
The therapeutic range of paracetamol is 66-132 μmol/lit. Most of the paracetamol taken in the body (~90-95% of the therapeutic dose) is primarily metabolized in the liver and converted to inactive metabolite by conjugation with sulfate and glucuronide (Scheme 6), and then excreted by the kidneys through urine.

b) Danger Mode Metabolism
Only a small portion (~5-10% of the therapeutic dose) is metabolized by the hepatic cytochrome P450 i.e. CYP450 enzyme system (more specifically CYP450 2E1 and CYP450 1A2) to N-acetyl-p-benzoquinone imine (NAPQI), which, if allowed to accumulate is toxic to the liver and may be fatal in extreme cases. Normally NAPQI is detoxified by reacting irreversibly with the sulfhydryl groups of glutathione in liver and the harmless product are excreted in the urine. But in case of paracetamol-toxicity, when the above-mentioned safe mode sulfate and glucuronide pathways become saturated, more paracetamol is converted to NAPQI. As a result of which the supply of glutathione in the liver store become exhausted and hence the NAPQI is now free to attack the cell proteins, resulting the widespread hepatocyte damage of liver causing acute hepatic necrosis and ultimately death. It is observed that prolonged fasting, regular consumption of excessive alcohol or concurrent use of drugs increase the risk factors for developing hepatic toxicity as the above factors induce CYP450, especially CYP450 2E1.

9. ADVANTAGES OVER NSAIDs
Paracetamol has been excluded from the class of NSAIDs due to its very little anti-inflammatory properties. Again, it does not affect the function of kidneys and blood coagulation as those of NSAIDs and moreover it does not cause any irritation in stomach in recommended doses. Paracetamol is also safe in pregnancy while the NSAIDs are responsible for high (~80%) risk of miscarriage (Li et al., 2003).

10. APPLICABILITY
a) Paracetamol is mainly prescribed for pain-relief (analgesic) and fever-relief (antipyretic) actions.

b) Paracetamol may be used by those who are suffering from peptic ulcers and asthma.

c) Paracetamol products may be used during pregnancy (although it is advisable to take always doctor’s opinion at this stage) and by the mothers who are breast feeding.

d) Due to the effectiveness and lack of side-effects in recommended doses, paracetamol products are frequently prescribed.

e) Particularly paracetamol products in recommended doses are suitable for all age group of people from elderly to young baby and this makes this drug so popular that it is available for purchase as an over-the-counter (OTC) medicine both in pharmacies or even grocer’s shop.

f) Aspirin is a highly effective analgesic and is used in treating mild to moderate pain like headaches as well as in some forms of severe chronic pain. Due to better tolerability, aspirin still has a significant role in the treatment of diseases such as rheumatoid arthritis, juvenile rheumatoid arthritis, osteoarthritis and spondyloarthropathies.

g) The major uses of aspirin (doses 50mg-100mg) today are in the primary and secondary prevention of cardiovascular diseases. Aspirin as an effective antithrombotic agent, at a dose of 75 mg daily in people with occlusive vascular disease (secondary prophylaxis) reduces the risk of non-fatal myocardial infarction (MI) and the use of low dose aspirin (primary prophylaxis) in people without pre-existing occlusive vascular disease, maintains the balance between the absolute thrombotic risk of developing cardiovascular disease (defined as non-fatal MI, stroke, coronary and stroke death, and new angina) and the haemorrhagic risk to the patient. Aspirin is observed to be efficient in reducing the risk of thromboembolic stroke.

h) Several retrospective studies have shown that prophylactic long-term use of aspirin daily, and to a lesser extent NSAIDs, is associated with a halving in the risk of developing colorectal cancer. Other studies show that aspirin or NSAIDs may be protective against gastric cancer, and possibly against cancers of the oesophagus, prostate, ovary, breast and lung.

i) Low dose aspirin and other NSAIDs may protect against dementia of vascular and/or Alzheimer’s type.
j) Combined treatment with aspirin (75 mg) and unfractionated heparin in pregnant women with a history of recurrent miscarriages and antiphospholipid antibodies is standard care. Low-dose aspirin (75 mg) reduces the risk of pre-eclampsia by around 15% for women at both low and high risk, with a similar reduction in the risk of perinatal death.

Aspirin may also be used for the following cases on which research is still ongoing but results from some studies done so far show promise in the use of aspirin for the following indications: migraine treatment, prevention of cataracts, improving circulation in gums, prevention of adult leukemia, prevention of HIV replication, increasing success rates of invitro fertilization (IVF) programmes.

11. ADVERSE EFFECTS AND TREATMENT
The recommended dose of paracetamol is two 550 mg of tablets (for adults), with four hours between doses and no more that obviously no more than eight tablets in 24 hours. The overdose of paracetamol may cause liver damage, hepatic necrosis and ultimately death if the concerned patient is not treated within proper time limit (Lubel et al., 2007). For this overdose treatment two antidotes namely methionine and N-acetylcysteine can be used which can boost levels the vital glutathione in the liver. About 3 % adult people suffer from gastrointestinal bleeding problems for taking aspirin. It also creates ringing in ears, hallucinations, seizure etc. About 10-30 asthmatic patients are sensitive to aspirin. It is also harmful to the heart of unborn baby. Overdose toxicity is treated with activated charcoal, intravenous dextrose and normal saline, sodium bicarbonate, and dialysis.

Caution!! Always take proper advice from Doctor(s) before using such drugs.

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REFERENCE