



# A Review on Preparation, Properties and Uses of Paracetamol

Abhinandan Jain<sup>1,2,\*</sup>

<sup>1</sup> Assistant Professor, Department of Chemistry, Sidharth Govt. College, Nadaun, H.P-177033, India.

<sup>\*2</sup> Department of Physical Sciences, Sant Baba Bhag Singh University, Jalandhar, Punjab-144030, India.

## ABSTRACT

Paracetamol (Acetaminophen) has analgesic and antipyretic effects. It comprises a significant role in all age groups in all over the world due to its first choice for the cure of fever with mild pain. It is low cost and easily available drug. It has clinical pharmacological activities including high antipyretic and analgesic activity and no or low anti-inflammatory activity as well as minor renal, gastrointestinal, and vascular side effects. This paper summarizes preparation methods, physical and chemical properties and medical uses of Paracetamol. In future, some new findings must be there for best clinical use as well as preventing the damage to kidney and liver due to improper dosage of it.

**Keywords:** Acetaminophen, Analgesics, Antipyretic, Preparation, Physical and Chemical properties, Uses, Paracetamol

## Introduction

Paracetamol (acetaminophen) is one of the most commonly used drug both over the counter and on prescription drug in the world for fever and pain for almost all ages [1]. It is low cost and easily available drug. It is a weak acid (pKa 9.7), and is therefore, unionized at pH values [2]. It has clinical pharmacological activities including high antipyretic and analgesic activity and no or low anti-inflammatory activity as well as minor renal, gastrointestinal, and vascular side effects (Table 1). The World Health Organization (WHO) has included paracetamol drug in its list of essential medicines ("the most efficacious, safe and cost-effective medicines for priority conditions") [3]. The analgesic action of paracetamol has been recognized to its inhibition of the cyclooxygenase (COX) pathway in the central nervous system (CNS), falling the manufacture of pain-mediating prostaglandins, but it may also increase endocannabinoid transmission and amend diminishing serotonergic inhibitory pathways [4].

**Table 1. Clinical pharmacological activities of paracetamol**

Antipyretic	High activity
Analgesic	High activity
Antiplatelet	Low activity
Anti-inflammatory	Low activity
Antidepressant	Anecdotal
Cognitive-enhancer	Anecdotal

### Preparation of Paracetamol

There are different methods for synthesis of Paracetamol and they are:

**1) Classical method:** This classical method for Paracetamol's production involves first step acetylation of 4-aminophenol with acetic anhydride as the last step.. There is acetylation to 4-aminophenol along with acetic anhydride. The preparation of 4-aminophenol is different. One of the methods is the nitration of phenol along with nitric acid afford 4-nitrophenol that is reduced to 4-aminophenol by the hydrogenation over Raney's nickel. In second method, nitrobenzene is reduced electrolytically that gives 4-aminophenol directly.

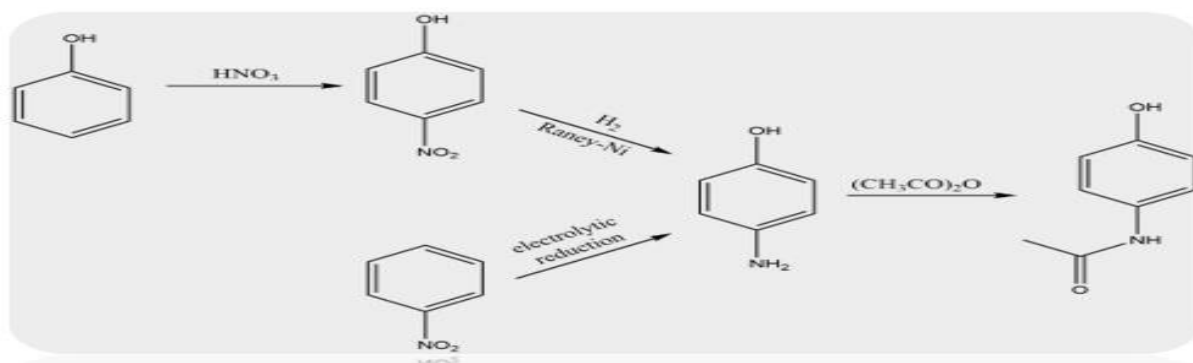


Figure 1: Synthesis of Paracetamol by the Classical method [5].

**2) Synthesis of Celanese:** There is an alternative industrial synthesis developed over the Celanese which involves firstly phenol's acylation with acetic anhydride in the presence of hydrogen fluoride (HF) which give ketone, then ketone convert to ketoxime with hydroxylamine and ketoxime convert to para-acetylaminophenol by acid-catalyzed Beckmann rearrangement.

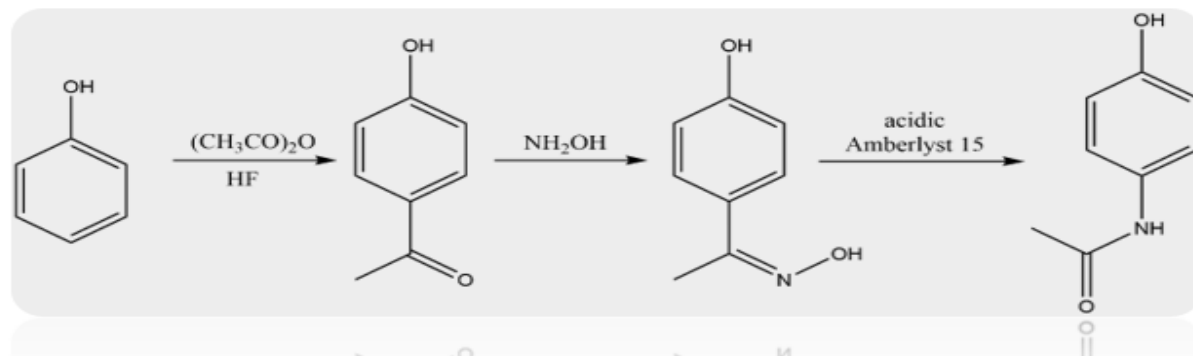


Figure 2: Synthesis of Paracetamol by the Celanese [5].

**3) From p- NitroChloroBenzene:** When p-nitro chloro benzene is treated with caustic soda at temperature of  $150^\circ\text{C}$  and pressure of  $5\text{kg/sq.cm}$  for 8 hours in an autoclave, p-nitro phenol (PNP) as a product is formed, separated by crystallization followed by filtration. Further, p-nitro phenol (PNP) is reacted with acetic acid at  $\text{pH}=3$  followed by reduction and product, p-amino phenol (PAP) is formed. Finally, p-amino phenol is acetylated and Paracetamol is formed, followed by product is bleached with Activated carbon to produce snow white colour, Paracetamol and then dried in a tray dryer and ground to the size of 40 microns [6].

**Table 2. Physical Properties of paracetamol**

<b>Alternate names</b>	Acetaminophen, p-Hydroxyacetanilide, , N-para hydroxyphenylacetamide, p-acetyl aminophenol
<b>Chemical formula</b>	C <sub>8</sub> H <sub>9</sub> NO <sub>2</sub>
<b>Appearance</b>	White odourless crystalline powder; large monoclinic prisms from water
<b>Molecular weight</b>	151.16
<b>Melting point</b>	169-170.5°C
<b>pH</b>	5.3 to 6.5 at 25°C.
<b>Density</b>	1.293gm/cc
<b>Dissociation constant</b>	pKa = 9.0-9.5
<b>Partition coefficient</b>	Pc = 6.237 (octanol: pH 7.2 buffer)
<b>Stability</b>	Dry, pure paracetamol is stable to 45°C.
<b>Solubility</b>	Soluble in water(1:70,1:20 at 100°C), ethanol(1:7), acetone(1:13),chloroform(1:50),glycerol(1:40),methanol(1:10),propylene glycol (1:9) and solutions of alkali hydroxides; insoluble in diethylether Slightly soluble in ether. It is insoluble in petroleum ethers and benzene.

### Chemical Properties of Paracetamol

Due to the presence of hydroxyl functional groups, Paracetamol (p-Hydroxyacetanilide) gives usual reactions of Phenols. It undergoes some reactions like oxidation, acetylation, with sodium hydroxide and also gives iron (iii) chloride test for the detection of phenolic group [7]. Further, Other chemical reactions that paracetamol undergo are:

#### 1) Formation of N-acetyl-p-benzoquinoneimine(NAPQI)

When N-oxidation of paracetamol is done, N-hydroxyparacetamol is formed, followed by dehydration produces N-acetyl-p-benzoquinoneimine (NAPQI), a toxic intermediate.

#### 2) Formation of 4-hydroxy-N-carboxylalanine

On treatment of Paracetamol (p-Hydroxyacetanilide) with acidified dichromate solution, 4-hydroxy-N-carboxylalanine is formed as product involving an oxidation reaction of the amide functional group [7].

#### 3) Titration with Ammonium Cerium (iv) Sulphate

The analysis of paracetamol is done by British pharmacopoeia method that involves heating of paracetamol with 1moldm<sup>-3</sup> sulphuric acid under reflux and 4-aminophenol is formed followed by titrated it with ammonium cerium (iv) sulphate an oxidizing agent, using ferroin as an indicator [8]. Firstly, it oxidizes 4-aminophenol to the iminoquinone completely and then, oxidize the ferroin indicator from Fe<sup>2+</sup> to Fe<sup>3+</sup> (ferriin). During the titration, the solution should be red, and the yellow end point is the transition from red to pale blue.

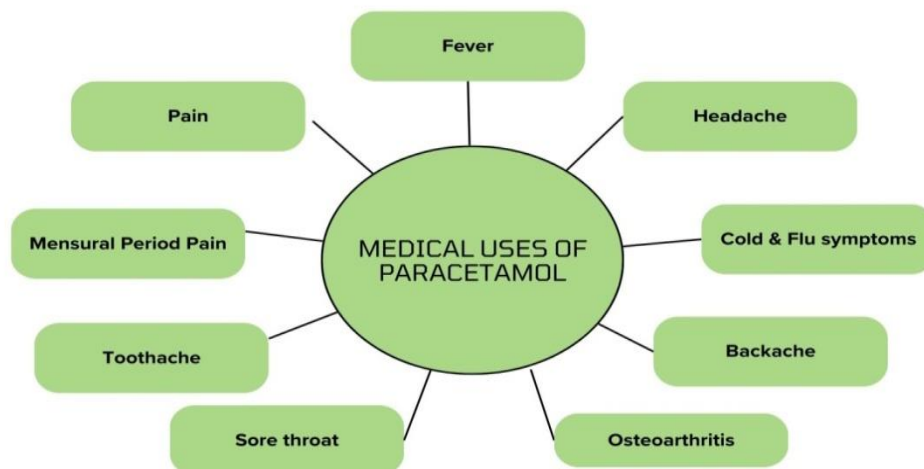
#### Dosage of Paracetamol

It is usually recommended to read out the dosing instructions given on the package of medications purchased during self-medications. For children, dosing of medications is given on the basis of weight of the child. According to the Tylenol professional product monograph, "for adults and children 12 years of age and older, the recommended dose of acetaminophen is 650 to 1000mg every 4 to 6 hours as required, not to exceed 4000mg in 24 hours... For children under 12 years of age, the recommended dose of acetaminophen is 10 to 15mg/kg every 4 to 6 hours, not to exceed 5 doses (50 to 75mg/kg) in 24 hours." It should be noted that for infants and

children, different concentrations of acetaminophen in liquid is available, therefore, it is advised to read out instructions very carefully and consult the doctor about the doses. [9, 10].

### Medical uses of Paracetamol

There are many medical uses of Paracetamol (Figure 3) like in reduction of fever, headache, cold&flu, backache, menstrual period pain, toothache, osteoarthritis, sore throat etc.



**Figure 3: Medical uses of Paracetamol**

### Conclusion

Paracetamol is one of the known and recognized drug both over the counter and on prescription. This paper aims to highlight preparation methods, physical and chemical properties and medical uses of Paracetamol. It has analgesics and antipyretic effects. It is low cost and safe to use. It is used for mild and moderate pain. Paracetamol has a good safety report that leading for maximum importance across all age groups in all over the world. Though, Paracetamol have disadvantages also. Overdose of paracetamol leads to kidney and liver damage.

### References

- [1] Moore, R.A.; Moore, N. Paracetamol and pain: The kiloton problem. *Eur. J. Hosp. Pharm.* 2016, 23, 187–188. [CrossRef] [PubMed]
- [2] Cooper, D., et al., Editors. *Comprehensive Medicinal Chemistry*. 1990, Oxford: Pergamon.
- [3] World Health Organization. WHO model list of essential medicines, 21st list. July 2019. <https://www.who.int/publications/i/item/WHOMV-PEMPI-AU2019.06> (viewed July 2019).
- [4] Sharma CV, Mehta V. Paracetamol: mechanisms and updates. *Continuing Education in Anaesthesia Critical Care and Pain* 2014; 14: 153–158.
- [5] Wikipedia. Paracetamol. [Online].
- [6] K. Ashutosh, New Age International (P) limited, Publishers, New delhi, 2004, 83-89.
- [7] E. Frank, Royal Society of Chemistry, London, 2002, 1-13.
- [8] IARC, IARC Monograph on Paracetamol (Acetaminophen): An Updating of IARC Monographs, 1990, 1-50, 307-309.
- [9] A. K. Przybyl, J. Kurek, *Laboratory of Organic Chemistry –Natural products and pharmaceuticals*, 2013, 5-6.
- [10] N. G. Swarooparani, *International Journal of Chemical and Physical Sciences*, 2015, 8 (4), 289-294.