جامعة الانبار

كلية : الصيدلة

قسم : الكيمياء الصيدلانية

اسم المادة باللغة العربية: الكيمياء العضوية

اسم المدة باللغة الإنكليزية**Organic Chemistry lab**

المرحلة: الثالثة

التدريسي: د. سمر عدنان احمد

عنوان المحاضرة باللغة العربية: تجربة تحضير الاسيتوفين

عنوان المحاضرة باللغة الإنكليزية: **Synthesis of Acetaminophen**

Synthesis of Acetaminophen

Analgesics are compounds used to reduce pain, antipyretics are compounds used to reduce fever. One popular drug that does both is aspirin, another is acetaminophen which is often used by people who have unwanted, harmful side effects to aspirin. Acetaminophen, which can be synthesized from p-aminophenol, is probably best recognized under the trade name Tylenol.

Acetaminophen (paracetamol) is a synthetic non-opioid derivative of p-aminophenol and basic bioactive molecule in numerous pharmaceutical preparations for the treatment of colds and flu. In combination with opioid analgesics, acetaminophen can also be used in the management of more severe pain such as post-surgical pain and providing palliative care in advanced cancer patients. Design of synthesis of acetaminophen is based on a modern approach of choosing the right synthetic route and using methods necessary for the characterization of the resulting pharmaceutically active compound, thereby providing reliable parameters of the chemical quality of the synthesized molecules.

Formation of the preferred form of acetaminophen is a process made up of two stages, where in the first stage an acid catalyzed reaction gives the crude acetaminophen. The reaction takes place according to the mechanism of nucleophilic addition in which the

nitrogen atom of the p aminophenol as nucleophile by attacking a carbonyl group of acetic anhydride forms an intermediate which undergoes the further elimination of the acetate anion. Recrystallization is one of the most common techniques used for purifying drug solids. One of the goals of this study was to achieve the results through the crystallization process in optimum conditions, in order to improve the yield and adequate purity of synthesized acetaminophen. In pharmaceuticals cyclodextrins have mainly been used as complexing agents to increase the aqueous solubility of poorly water-soluble drugs through noncovalent inclusion complexation and to increase their bioavailability and stability. Complexation with beta cyclodextrin was attempted to improve solubility of acetaminophen.

N-acylated aromatic amines (that have the acyl group bonded to the nitrogen atom) such as phenacetin and acetaminophen are mild analgesics and antipyretics which can be obtained without a prescription. Acetaminophen is the basic bioactive molecule in a number of pharmaceutical preparations against colds and flu, such as Tylenol and Panadol (Fig. 1.). Acetaminophen (paracetamol) or according to IUPAC N-(4-hydroxyphenyl) ethanamide belongs to the antipyretic non-opioid analgesic, molecular formula C8H9NO2 and mass (151.18 g / mol).

The molecule consists of a benzene nucleus substituted by a hydroxyl group and the nitrogen atom of the amide group in the para (1,4) position 2. The presence of two active groups also gives to the benzene nucleus high reactivity during electrophilic aromatic substitution.

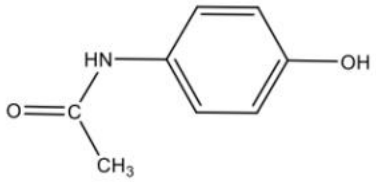


Figure 1: Molecular structure of acetaminophen [*N-(4-hydroxyphenyl) acetamide]*

pKa of acetaminophen is 9.70 and is classified as a weak acid. Acetaminophen is present in the form of crystalline white powder, odorless, with a slightly bitter taste. The crystals formed from a saturated aqueous solution, have the form of monoclinic prisms. The concentrated aqueous solution of acetaminophen has a pH of 5.5 to 6.5. According to BCS classification system of drugs it belongs to the class III, which is characterized by high solubility and low permeability 4. The values of melting point of acetaminophen are in the range of (168-172 ^{o}C).

Acetaminophen is poorly soluble in cold water (1.4 g / 100 ml), in hot water solubility is higher and amounts to about (5 g/100 ml). It has a low solubility in non-polar (toluene, pentane, benzene, petroleum ether) and chlorinated hydrocarbons (CCl4). It shows a significant solubility in solvents of moderate polarity N, N

dimethylformamide, alcohols and diethylamine. It exists in five polymorphic forms (of which two can only be accessed at high pressure). Form I (Fig 2.) displays a herringbone arrangement of molecules within the crystal structure, whilst form II is layered

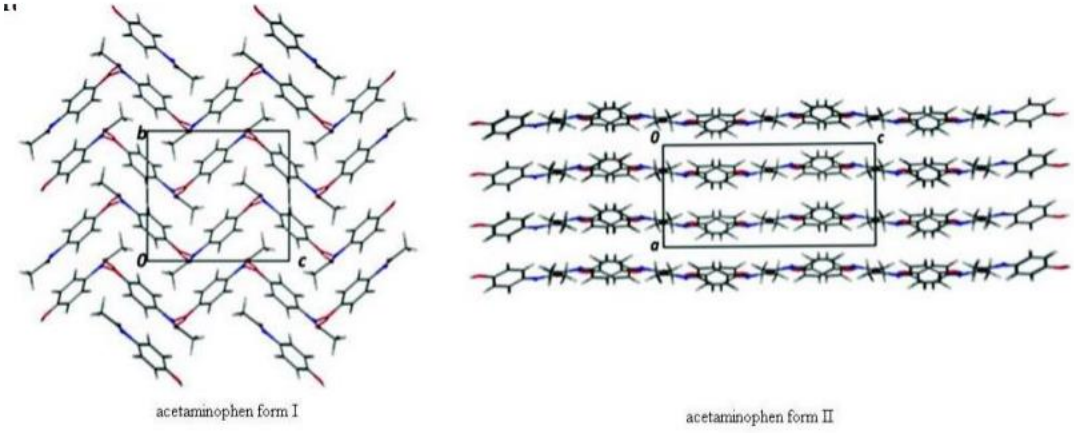


Figure 2: The polymorphic forms of Acetaminophen

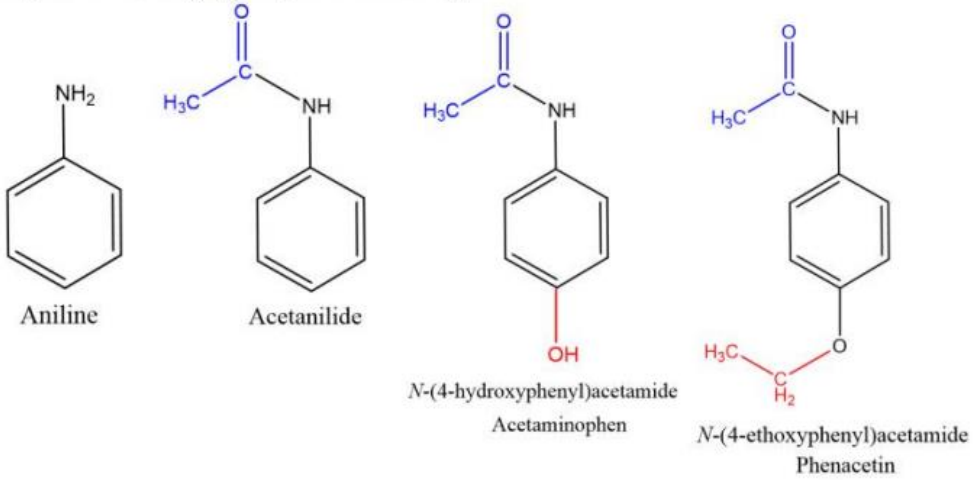
Because of the commercial importance, we have paid the attention to the synthesis and purity of acetaminophen. The ideal synthesis of a compound would be the one that includes translating the most widespread and cheapest starting material in the desired molecule, including the smallest possible number of phases with the most accessible reagents and the highest possible total yield. The important stage in the manufacture of pharmaceutically active compounds is crystallization from a solution. Over 90% of all pharmaceutical products such as tablets, capsules, etc., include a pharmaceutically active substance in the solid state.

The overall success of the formulation process and the results of the mechanical properties of tablets, largely depend on the quality of crystal substances used during the tableting process. The term crystallization usually involves the formation of the crystalline form of a particular solution, whilst broader definition includes the precipitation process and the transformation of a solid state. Methods of crystallization include the use of certain solvents, but different crystallization conditions may lead to the occurrence of different crystal forms.

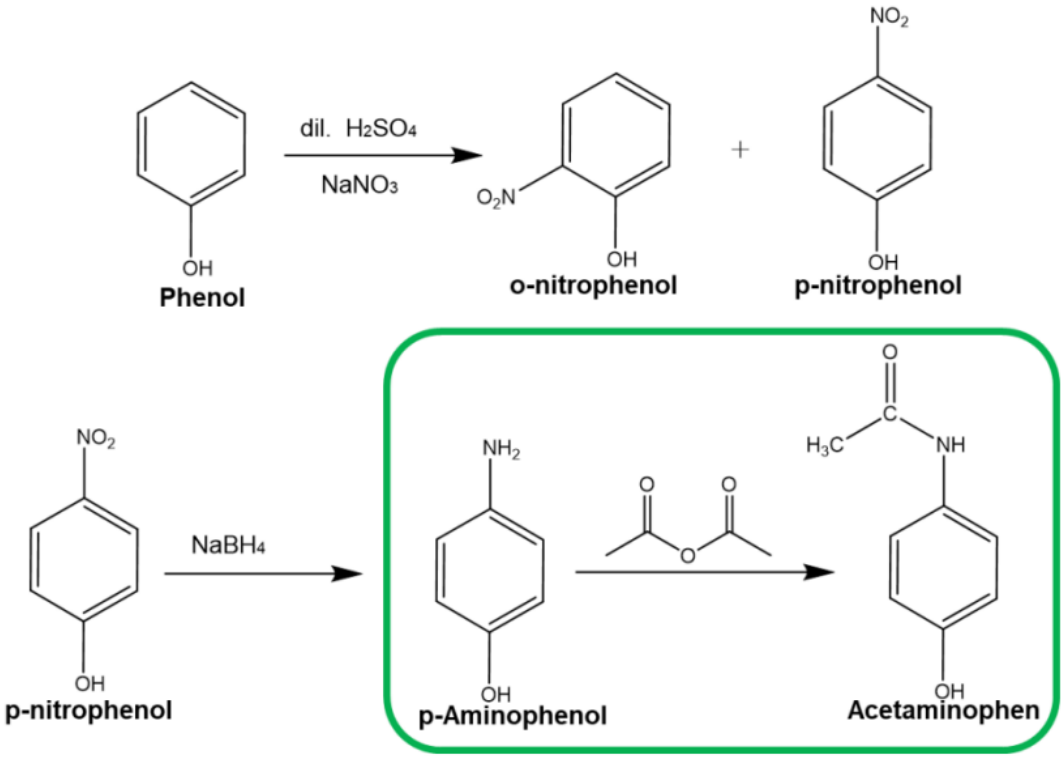
We are constantly working on researches and finding new, innovative methods of manipulation of crystallization process 10. Design of synthetic route of acetaminophen is based on four different laboratory methods of producing the crude acetaminophen by nucleophilic addition mechanism, followed by elimination.

- ***What is Acetylation?***

Acetylation simply involves the addition of an acetyl group to a compound. An acetyl group is made up of a carbonyl group with a methyl



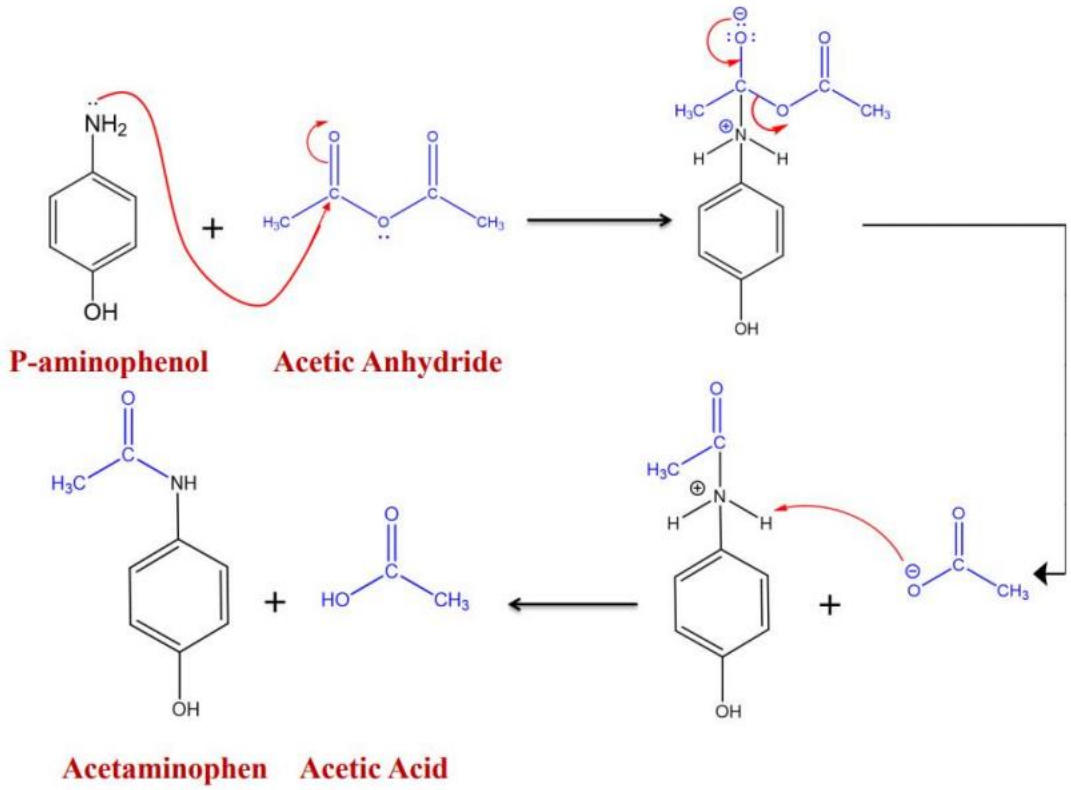
Phenol undergoes nitration yielding a mixture of o-nitrophenol and p-nitrophenol. • After p-Nitrophenol is separated, it is reduced by using Sodium borohyd ride (NaBH4). • p-Aminophenol is produced and acetylated by using acetic anhydride which produces Acetaminophen.



Acetaminophen Synthesis Mechanism The synthesis of Acetaminophen is based on the amine group of p aminophenol being acetylated by acetic anhydride to form an amide functional group. p-aminophenol is a bifunctional compound, containing both a phenol and an amine.

N-acylation mechanism leading to the synthesis of acetaminophen (amide) involves a nucleophilic attack by the lone pair on nitrogen

in 4-aminophenol on the carbonyl carbon of the symmetric acetic anhydride. The attack results in a tetrahedral carbon containing structure putting a positive charge on the nitrogen and a negative charge on one of the oxygen atoms. The negative charge on the oxygen "comes down" and forms a double bond with the carbon causing the acetate ion to leave. The acetate ion then attacks the extra hydrogen attached to the nitrogen, forming acetic acid and acetaminophen



Practical Section:

Procedure:

1) In a round-bottomed flask (100 mL) place 1.375 g of p aminophenol, and then add 3.75 mL of distilled water.

2) To this mixture, drop carefully 1.5 mL of acetic anhydride. Adjust the Liebig condenser and heat under reflux for 20 minutes at (115-120 C)

3) After the substrate has dissolved, cool down the solution by placing the round-bottomed flask in an ice-bath for few minutes, then in the freezer for 10-15 minutes, and the crystals of product should appear in the flask.

4) Filter the product on the Büchner funnel and wash with cold water. Dry on air on Petri dish.

Safety Precautions:

• Acetic anhydride is corrosive and its vapor is irritating to the respiratory system. Avoid skin contact and inhalation of the vapors. In the event of skin contact, rinse well with cold water. If the vapors are inhaled, move to an area where fresh air is available.

• P-aminophenol is harmful by inhalation and by contact with the skin. In the event of skin contact, rinse well with cold water. If the vapors are inhaled, move to an area where fresh air is available.