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PAIN RELIEF FOR EVERYBODY:
LARGE SCALE PRODUCTION OF ASPIRIN

Aspirin, otherwise known as acetylsalicylic acid, was first introduced to the public in 1899. Today, worldwide sales of aspirin are about 50,000 tons per year, giving pain relief to millions every day. Americans alone consume $29 billion worth of aspirin every year. Large-scale production of aspirin provides a highly valuable contribution to health throughout the world.

In ancient Greece, Hippocrates used leaves from a willow tree to brew a tea that relieved the pain for women in childbirth; much later, it was shown that these leaves contain aspirin. In 1763, Oxford's Reverend Edward Stone gave dried bark of the willow tree to 50 parishioners suffering from rheumatic fever. In 1823 Italy, the main ingredient of aspirin was extracted from the willow tree and named salicin. Salicin is an alcoholic β-glycoside. Swiss and German researchers also discovered salicin in meadowsweet flowers. Charles Frederic Gerhardt, a French chemist, first synthesized aspirin in 1853. In 1897 Germany, Bayer Company's Felix Hoffmann received approval for a trademark and developed a process for synthesizing acetyl salicylic acid, leading to clinical trials. In 1899, these clinical trials were successfully completed and Aspirin was launched commercially for the first time.

How does aspirin work?

Aspirin relieves pain by reducing inflammation. Acetylsalicylic acid binds to an enzyme called cyloocygenase-2 in cells, which are produced in large quantities in damaged cells and cause pain. Without the presence of acetylsalicylic acid, the cylooxygenase-2 enzyme makes prostaglandins, which send messages to the brain that part of the body is in pain. They also cause the damaged area to release fluid from its blood so that it will swell up or inflame. This swelling protects the damaged cells from further damage by creating a cushion. When aspirin is present, the enzyme is no longer able to make prostaglandins. Therefore, some of the pain messages are not sent to the brain; less pain follows because there is a decrease in inflammation. The Bayer Company derived the name "aspirin" by taking the 'A' in acetyl chloride and the "spir" in spiraea ulmaria (the plant source for salicylic acid) and the "in" because it is a familiar ending for medicine names.

Acetylsalicylic acid is $C_9H_8O_4$; its structure is shown in Figure 1. In 1971, it was discovered that this organic compound inhibits enzymes from converting acid to prostaglandin, a member of a group of lipid compounds derived from essential fatty acids, that perform many important functions in the body. When aspirin is dissolved in water, the solution is acidic. However, because aspirin is a weak acid, it does not have significant acidic properties.

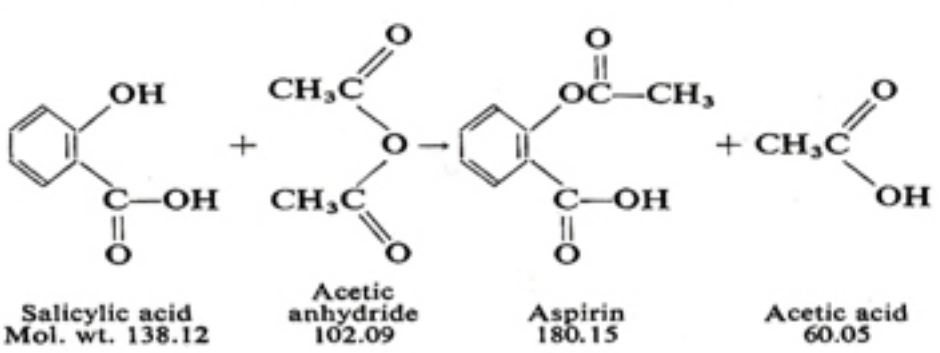

FIGURE 1: Synthesis of Aspirin

Acetylation, also called ethanoylation in IUPAC (International Union of Pure and Applied Chemistry) nomenclature, is a reaction that introduces an acetyl functional group into an organic compound. Aspirin synthesis is a substitution reaction where the OH group from salicylic acid reacts with an acid to form an ester, acetylsalicylic acid. Aspirin is prepared by the esterification of the phenolic hydroxyl group of salicylic acid. The process to prepare salicylic acid from phenol was discovered by the German chemist Hermann Kolbe. In the Kolbe synthesis (or Kolbe-Schmitt reaction), sodium phenoxide is heated with CO_2 under pressure; the resulting mixture reacts with sulfuric acid to yield salicylic acid.

Laboratory-scale Production of Aspirin

For laboratory-scale synthesis, 5 grams of salicylic acid is added to 120 mL of water in a flask. Then, 5mL of acetic anhydride is added plus 0.5 mL of aqueous phosphoric acid solution as a catalyst. The flask is heated in a water bath where the contents are agitated using a laboratory stirrer. The flask is heated under reflux for about one hour. When the solution cools, crystals of aspirin form; these are filtered and possibly re-

crystallized. A good yield would be about 5 to 6 grams and the remaining solution is discarded.

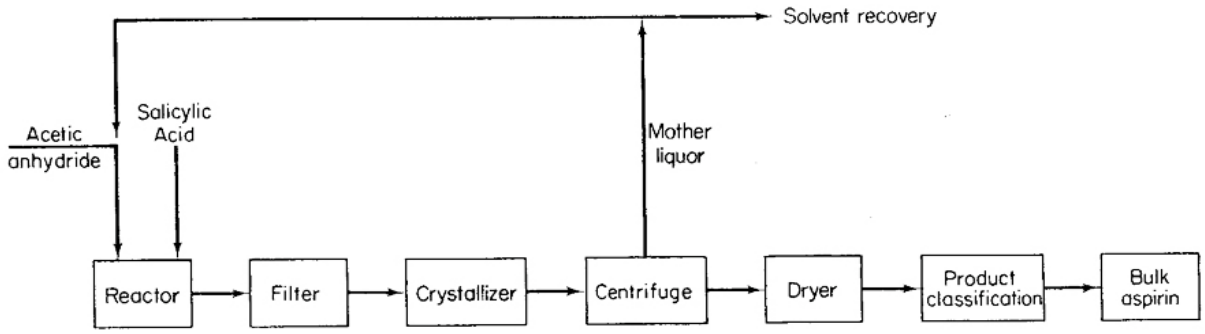

FIGURE 2: A Typical Large-Scale Process Flow Diagram for Aspirin

Large-scale Production of Aspirin

In a large-scale industrial process, grams are replaced with tons. First, the required raw materials are stored for about two weeks of production. Solid salicylic acid is placed in a storage silo whereas acetic anhydride, a combustible corrosive liquid sensitive to water, is kept in a closed corrosion-resistant tank. To transport the materials to the reactor, a screw conveyor (an Archimedean screw contained within a tube and turned by a motor to deliver material from one end of the conveyor to the other) is used for salicylic acid while a system of pumps and pipes provide for acetic anhydride.

The reactor contains 120 tons of water, acetic anhydride, and salicylic acid. An agitator provides necessary mixing. A common method for heating is to pass steam through the vessel's outer jacket. Then the mixture is pumped to a crystallizer and then to a filter to yield approximately 5.5 tons of aspirin that is subsequently dried and stored. The drying process requires significant energy.

Waste from making aspirin cannot be poured down the sink as is done in a small laboratory. The remaining solution contains un-reacted salicylic acid along with about 3 tons of acetic acid, which must be recovered and recycled, to make acetic anhydride. The phosphoric acid can be recovered or neutralized with alkali before disposal. Therefore, after the aspirin is made, additional equipment is required to recover valuable chemicals and to protect the environment. Normally, solvents other than water are recovered by distillation; in addition, water is recycled if economically feasible.

The process required to make industrial-scale aspirin may run as a batch process where periodically reactors are filled and emptied. Alternatively, the process can be continuous where the reactants are fed at a fixed rate. For economic reasons, production of industrial-scale aspirin usually prefers the batch process.

Commercially, aspirin is available in four types: the generic brand, children's aspirin, regular strength, and buffered aspirin. Buffered aspirin can be made with $CaCO_3$; its pH level is much higher than that for the other types. Because aspirin suppresses the production of prostaglandins, capillaries in the stomach lining may leak. The amount of bleeding is minimal for most people but in some cases it can result in serious blood loss. The buffered aspirin prevents the aspirin from dissolving until it reaches the small intestine to reduce bleeding in the stomach.

Since its introduction in the United States, aspirin has experienced substantial growth. From 1949 to 1969, the annual production of aspirin increased from 10 million to 37 million pounds per year, With several major companies producing aspirin (Dow, Monsanto, Norwich, and Sterling), the production capacity in the United States has stabilized to approximately 45 million pounds/year. According to the Encyclopedia of

Chemical Processing and Design, annual aspirin consumption per capita in the United States has grown from 55 5-grain tablets in 1940 to over 220 5-grain tablets in the 1970s. There has not been much growth since then. In Chester Nelson Mitchell's book, The Drug Solution, he concluded that in 1990, US per capita aspirin consumption was 225 5-grain tablets per year.

Aspirin is considered to be the most effective, low-cost painkiller available for over-the-counter sale. Many doctors encourage their elderly patients to take one baby aspirin every evening because aspirin is believed to help prevent heart attacks and strokes. Along with inhibiting platelet aggregation, aspirin is a strong antipyretic, that is, a drug that reduces fever. Today a common household item, few truly appreciate its wide healing effects. Aspirin has attained a leading position worldwide as a prescription-free medicine for alleviating pain, inflammation, and fever. Thanks to chemistry and modern chemical technology, aspirin is now available to millions throughout the world. By relieving pain, aspirin has contributed to a better standard of living.