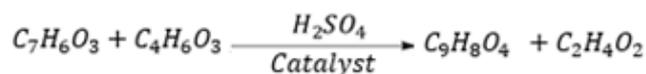


ASPIRIN MANUFACTURE - INFORMATION DOCUMENT

The Synthesis and the history of Aspirin

Acetylsalicylic acid; $C_9H_8O_4$ commonly known as aspirin is prescribed for its antipyretic, analgesic and anti-inflammatory properties. Aspirin is made from salicylic acid; $C_7H_6O_3$ and acetic anhydride; $C_4H_6O_3$. Sulfuric acid; H_2SO_4 is used as a catalyst and acetic acid is a by-product according to the reaction below:

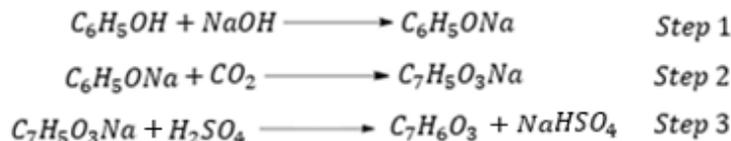


Salicylic acid, the major component in the reaction, was first extracted in 1835 from a plant called *Spiraea ulmaria*⁸. It was used to treat pain and fever⁴. Acetylation of salicylic acid in the above reaction was necessary because the plant extract irritated the stomach when ingested, often resulting in bleeding at large doses. Salicylic acid (SA) an organic compound and is used as an active ingredient in cosmetic products. It is a colorless crystal found naturally in the bark of the willow tree.

Salicylic acid can be produced using three synthetic routes. The first route is from phenol obtained from crude oil. The second route is from salicin extracted plants. The third route is from oil of wintergreen also found in plants.

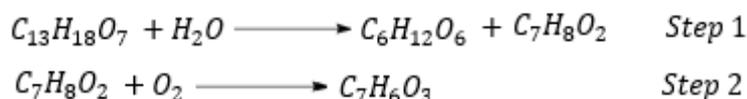
Salicylic acid from phenol - Route 1

When phenol, C_6H_5OH (obtained indirectly from crude oil) reacts with $NaOH$; a phenolate salt, C_6H_5ONa is formed. Heating the phenolate salt with carbon dioxide under high pressure results in the formation of salicylic acid. The multistep reaction is shown below:



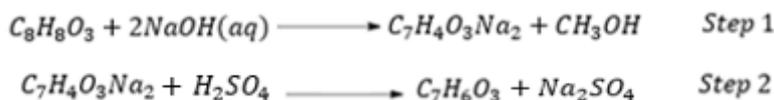
Salicylic acid from salicin - Route 2

Salicin, $C_{13}H_{18}O_7$ is found in the bark or stems of willow and meadow sweet trees. Salicin is extracted from the willow bark using alcohol (80%) and water (20%) solvents. Hydrolysis of salicin yields salicyl alcohol, $C_7H_8O_2$ and D-glucose, $C_6H_{12}O_6$ as a by-product. Salicyl alcohol is then oxidised to salicylic acid. The multistep reaction is shown below:



Salicylic acid from oil of wintergreen - Route 3

Salicylic acid produced by the hydrolysis of oil of wintergreen (methyl salicylate), $C_8H_8O_3$ which are derived from plants according to the two steps reaction below:



The Life Cycle Assessment

The Life Cycle of a product starts with the raw materials used to make it, flows through the processing of those resources in upstream processes used to make the precursors of the product, the manufacture of the product, its distribution, its use and what happens at the end of its life. Is it biodegradable or can it be recycled and become the resource for another product?

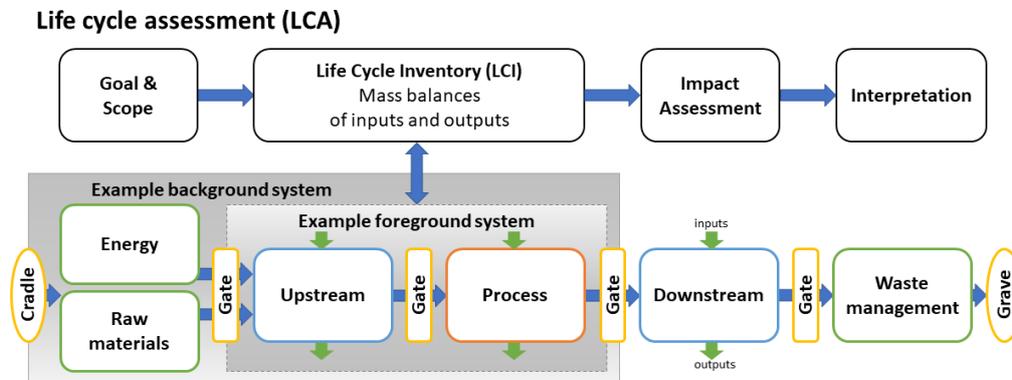


Figure 3: Life cycle assessment for chemical manufacturing processes. The assessment considers the full life cycle of the product from raw materials (cradle) to disposal after use (grave). To conduct a detailed life cycle inventory (LCI), which includes the mass balances for the processes under consideration, appropriate system boundaries (gate to gate) are chosen. The LCI will provide data to inform the choice, optimization and implementation of the process within the LCA⁶.

The Life Cycle Inventory is the quantitative part of the Life Cycle Assessment providing quantitative data for the impact assessment. Before conducting an LCI, we need to decide which part of the life cycle we are going to quantify. We cannot easily quantify across the entire life cycle from **cradle to grave**. Therefore, we choose the bits we are in control of to look at quantitatively and which will be assessed more qualitatively because the data may not be available and may be difficult to acquire. In other words, we choose boundaries for the quantitative analysis usually using a **gate-to-gate** approach.

Manufacture of aspirin

A. Industrial manufacture of aspirin

Salicylic acid is produced from crude oil or plants and acetic anhydride is produced from natural gas. Once synthesized, the two can then be combined to form aspirin as shown in Figure 2.

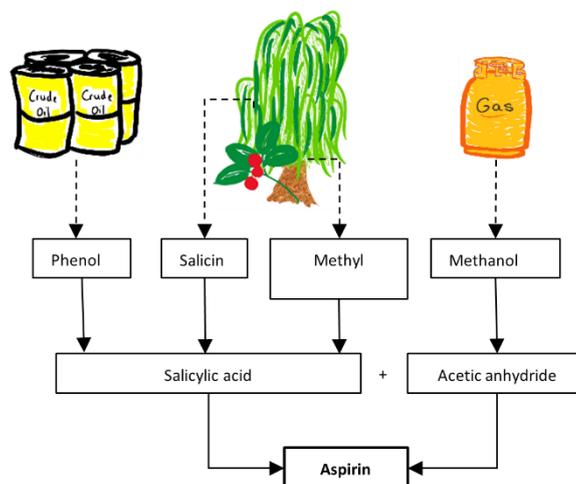


Figure 2: The flow diagram for the manufacture of aspirin

B. Synthesis of aspirin from salicylic acid and acetic anhydride in the laboratory

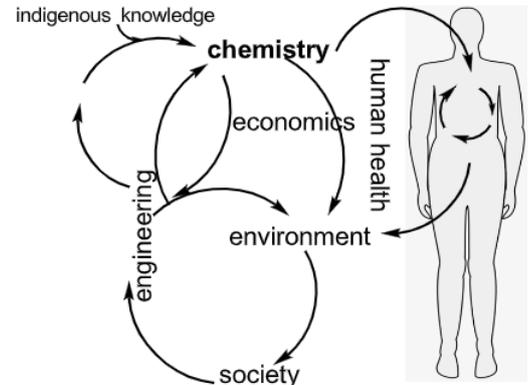
1. Weigh out approximately 1.0 g of salicylic acid (*record exact mass*), and transfer it to a clean, dry 6 inch test tube.
2. Use the dispenser to carefully add 1.5 mL of acetic anhydride to the salicylic acid. Then add 2 drops of concentrated sulfuric acid, H_2SO_4 , to the reaction mixture (*it acts as a catalyst and speeds up the reaction*). Put the test tube in a beaker of boiling water in a hood. Stir the mixture with a glass rod to break up any lumps. Once all the solid dissolves, heat five minutes longer.
3. Pour the contents of the test tube into a 50 mL Erlenmeyer flask containing 15 mL of water. Swirl the flask for a few minutes to mix the solutions and get rid of any unreacted acetic anhydride. (*The acetic anhydride reacts with water to produce acetic acid.*) Be sure that you are writing in your lab notebook.
4. Place the flask in an ice bath until a white solid crystallizes out. Occasionally a reaction will yield an oily product that resists crystallization. If that happens, scratch the bottom and sides of the flask with a glass stir rod to help start crystal formation, or warm the mixture just until the oil dissolves, and then re-cool
5. Allow 10 minutes for crystallization to occur. Meanwhile prepare a Buchner funnel and then filter the solid, being sure to use a trap flask between the Buchner funnel flask and the aspirator. Wash the solid with a small amount of **cold** distilled water.
6. Pour the liquid filtrate from the filter flask into a beaker. Add a scoop of $\text{NaHCO}_3(\text{s})$. After the bubbling subsides, discard this mixture down the sink with excess water.
7. Put a few crystals of your crude aspirin in a clean beaker. Label it as "crude aspirin." Let this air-dry until next week when you will take its melting point. Label the beaker, but do not cover it.
8. Scrape the rest of your aspirin product off the filter paper and dissolve it in about 3 mL of 95% ethanol in a 50 mL Erlenmeyer flask. If not all of your aspirin dissolves, take your flask to one of the hot water baths set up in the hood. Use tongs to hold your flask in the hot water. After a few moments, remove, and swirl. Repeat until all the solid dissolves.
9. When the aspirin has dissolved, add 10 mL of warm distilled water (*about 50 °C*). If any crystals form at this point, reheat the mixture in the water bath to re-dissolve them. Let the solution cool slowly with the mouth of the flask covered by a watch glass. When it is at room temperature, place it into the ice bath and leave it there a full ten minutes. Be sure that you are recording what you do and what you observe.
10. After crystallization is complete, filter the crystals in a Buchner funnel, wash them with a little ice-cold distilled water (*put your squeeze bottle in the ice*), and suction for several minutes. Discard the liquid filtrate down the drain with excess water. Scrape the solid onto a pre-weighed watch glass and put it in your drawer. Do not cover it because we want your product to finish drying by the next lab period.

THE ASPIRIN SYSTEM

A system consists of a collection of elements or components that are organized for a common purpose. The aspirin manufacture forms a part of the aspirin system, which includes engineering, the environment, society, human health, and economics.

The components that make up a drug system include:

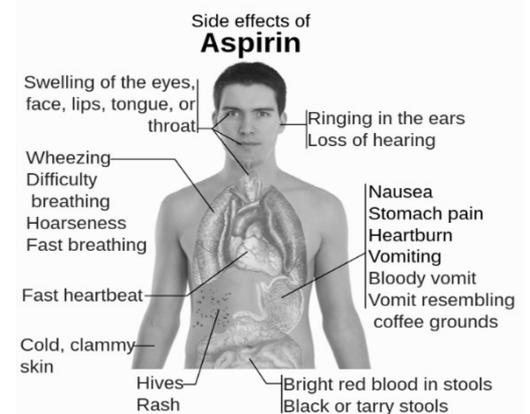
- The raw materials from the extraction phase.
- Any solvents, reagents and catalysts used during the reaction.
- The intermediate and by-products formed during a reaction.
- The energy requirements for the manufacturing process.
- Any waste materials released at any stage in the manufacturing process
- The economics associated job creation and contribution to Gross Domestic Product.
- The use of the drug and its effect on living organisms.
- The fate of the products of metabolism of the drug.
- The consumer and the environment around them.



The raw materials can be found from different sources, as shown by salicylic acid synthetic routes above. Reaction routes can differ, with some being more sustainable than others. Obtaining materials and suitable conditions for the aspirin synthesis will involve other sub-systems at different stages of the synthesis process. The packaging, use and disposal of end products of aspirin after manufacture or its metabolism after ingestion links the aspirin system to further systems, and this creates a web of interlinked systems between aspirin and associated systems. The ability to recognize the components that make up the aspirin system, and to view aspirin synthesis as a whole system itself, is an example of a systems thinking perspective.

Effects of aspirin on the human body

Aspirin is an effective anti-inflammatory and reduces fever¹. The medical uses of aspirin are applied in the cardiovascular system, the gastrointestinal system, oncology⁹ and other diseases. There are risks and complications associated with the use of aspirin. As an example, aspirin has been known to cause asthma attacks in patients with asthma. Aspirin also poses problems of drug resistance if used over a long period of time.



Green chemistry

Green chemistry goal is to minimize the environmental impact during the production and use of chemicals¹⁰ see Figure 4. To achieve these goals, it is important that we:

- Make better use of available resources for the development of a chemical process.
- Reduce waste generated in any preparation or handling of chemicals.

- Replace toxic reagents and products with environmentally friendly alternatives.
- Reduce the energy required to produce the desired products, either by the use of much faster processes or by the use of renewable energies involving lower energy cost with equal efficiency.
- Reduce the usage or generation of toxic compound substance
- Reduce costs by eliminating unnecessary steps



Figure 4: The goals of green chemistry

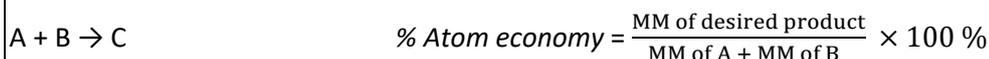
Green chemistry metrics

To assess the sustainability of a process, green chemistry metrics can be computed, and the results is used to evaluate the impacts of the process on the environment or human health. The purpose of the metrics is to quantify the efficiency or environmental performance of chemical processes. The greenness of the synthesis of salicylic acid using various routes can be assessed. It is important to note that once the salicylic acid has been manufactured, all synthesis routes converge as the salicylic acid now reacts with acetic anhydride to form aspirin.

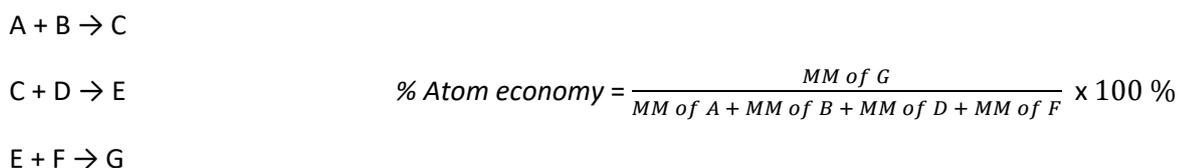
Some of the green chemistry metrics that can be calculated for the above process include³:

| Green chemistry metric and meaning | Equation |
|--|--|
| % <i>Atom economy</i> The number of atoms in the desired product to the atoms in the reactants. | $\frac{MM \text{ of the desired product}}{MM \text{ of all the reactants}} \times 100$ |
| % <i>Carbon efficiency</i> Carbon atoms in the desired product to the carbon atoms in the | $\frac{\text{carbon atoms in the desired product}}{\text{total carbon atoms in all the reactants}} \times 100$ |
| % <i>Mass efficiency</i> The mass of inputs to the mass of the desired product. | $\frac{\text{actual mass of the desired product}}{\text{total mass of all the reactants}} \times 100$ |
| % <i>Envirometal factor</i> The mass of the waste produced to the mass of the inputs. | $\frac{\text{mass of the waste produced}}{\text{total mass of all the reactants}}$ |
| % <i>Yield</i> The mass of the desired product to the expected mass desired product. | $\frac{\text{actual mass of the desired product}}{\text{theoretical mass of the desired product}} \times 100$ |

For a one-step reaction for the production of C:



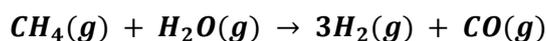
For a multi-step synthetic process for the production of G:



NB: If the stoichiometric relationships of reactants and products are not 1:1 then the coefficients of the species should be considered. Simply multiply the molar mass (MM) by the coefficients.

Worked out example:

Production of hydrogen gas from methane gas and steam according to the reaction:



% Atom economy

Calculate the % atom economy for the reaction.

Total MM of reactants = 16.0426 g + 18.02 g = 34.0626 g

Total MM of desired product (H₂) = 3 × 2.0158 = 6.0474 g

Note: There are 3 H₂ in the balanced equation.

$$\% \text{ Atom economy} = \frac{\text{MM of the desired product}}{\text{MM of all the reactants}} \times 100 = \frac{6.0474 \text{ g}}{34.0626 \text{ g}} \times 100 = 17.8 \%$$

% Carbon efficiency

Calculate the % carbon efficiency for the reaction.

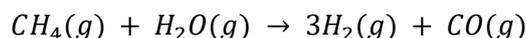
It measures the carbon atoms that end up in the product of interest in percentages.

$$\% \text{ Carbon efficiency} = \frac{\text{carbon atoms in the desired product}}{\text{total carbon atoms in all the reactants}} \times 100 = \frac{0}{1} \times 100 = 0\%$$

Note: There are no carbon atoms in the desired product (H₂).

% Reaction mass efficiency

When 22.6 g of methane reacts with 17.3 g steam according to the reaction, 5.62 g hydrogen gas is produced.



Calculate the % mass efficiency for the reaction.

It measures the exact mass of product of interest in percentages.

$$\% \text{ Mass efficiency} = \frac{\text{actual mass of the desired product}}{\text{total mass of all the reactants}} \times 100 = \frac{5.62 \text{ g H}_2}{39.9 \text{ g Reactants}} \times 100 = 14.1\%$$

% Yield

When 22.6 g of methane reacts with 17.3 g steam according to the reaction, 5.82 g of hydrogen gas is produced. The theoretical yield of H₂ is 5.82 g.

Calculate the % yield for the reaction.

It measures the exact mass of product of interest in percentages.

$$\% \text{ Yield} = \frac{\text{actual mass of the desired product}}{\text{expected mass of the desired product}} \times 100 = \frac{5.82 \text{ g H}_2}{5.82 \text{ g desired product}} \times 100 = 100 \%$$

DATA SHEET

Table 1: Material balance for the production of 1000 kg of salicylic acid from phenol

| COMPONENT | INPUTS (kg) | PRODUCT (kg) | WASTE (kg) |
|------------------|-------------|--------------|------------|
| Phenol | 927 | | 102 |
| Sodium hydroxide | 394 | | |
| Carbon dioxide | 589 | | 203 |
| Sulfuric acid | 497 | | 13 |
| Activated carbon | 184 | | 184 |
| Water | | | 178 |
| Sodium sulphate | | | 700 |
| Salicylic acid | | 1000 | 211 |

Table 2: Material inputs for the production of 1000 kg of salicylic acid from oil of wintergreen

| COMPONENT | INPUTS (kg) | PRODUCT (kg) | WASTE (kg) |
|--------------------|-------------|--------------|------------|
| Sodium hydroxide | 1380.74 | | |
| Sulfuric acid | 1691.40 | | |
| Oil of wintergreen | 1294.44 | | |
| Water | | | 155.33 |
| Salicylic acid | | 1000 | |
| Methanol | | | 231.88 |
| Sodium sulfate | | | 4901.61 |

Table 3: Material balance for the production of 1000 kg of methyl acetate from natural gas

| COMPONENT | INPUTS (kg) | PRODUCT (kg) | WASTE (kg) |
|----------------|-------------|--------------|------------|
| Methanol | 866.48 | | 434.07 |
| Water | | | 242.07 |
| Acetic acid | 1624.65 | | |
| Methyl acetate | | 1000 | 52 |

Table 4: Molar mass (MM) of compounds

| COMPOUND | FORMULA | MM (g/mol) | COMPOUND | FORMULA | MM (g/mol) |
|-------------------|-------------------|------------|---------------------|-----------------|------------|
| acetic acid | $C_2H_4O_2$ | 60 | salicylic acid | $C_7H_6O_3$ | 138 |
| acetic anhydride | $C_4H_6O_3$ | 102 | Salicyl alcohol | $C_7H_8O_2$ | 124 |
| aspirin | $C_9H_8O_4$ | 180 | sodium hydroxide | $NaOH$ | 40 |
| carbon dioxide | CO_2 | 44 | sodium phenoxide | C_6H_5NaO | 116 |
| d-glucose | $C_6H_{12}O_6$ | 180 | sodium salicylate | $C_7H_4O_3Na$ | 129 |
| methanol | CH_3OH | 32 | disodium salicylate | $C_7H_4O_3Na_2$ | 182 |
| methyl salicylate | $C_8H_8O_3$ | 150 | sodium sulfate | Na_2SO_4 | 142 |
| phenol | C_6H_5OH | 94 | sulfuric acid | H_2SO_4 | 98 |
| Salicin | $C_{13}H_{18}O_7$ | 286 | water | H_2O | 18 |

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