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Synthesis of Acetylsalicylic Acid – An Environmentally Friendly Approach

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ABSTRACT

Background: The aim of this study was to compare the yields of acetylsalicylic acid synthesis based on the traditional approach and the green chemistry approach. Green chemistry is one of the most important approaches in pharmaceutical sustainability. The reagents used for acetylsalicylic acid synthesis can be environmentally harmful, so there is a need for a better and safer alternative.

Methods: We conducted five syntheses based on the traditional approach and five syntheses based on the green chemistry approach. The synthesis process was identical except for one element – traditional synthesis uses sulfuric acid and green chemistry synthesis uses phosphoric acid. After synthesis, the theoretical and experimental yields were calculated. The obtained products were tested using high-performance liquid chromatography.

Main findings: The theoretical yield of acetylsalicylic acid in both reactions was determined as 3.896 g. Traditional synthesis gave us a mean yield of 3.113 g (79.8%). Green chemistry synthesis gave us a mean yield of 3.104 g (79.4%). The quality of both products was confirmed by the above-mentioned chromatography method. There was no statistically significant difference between the means of the product masses (p=0.8220).

Principal conclusions: Phosphoric acid can be used as a safe alternative to acetylsalicylic acid synthesis instead of sulfuric acid. As phosphoric acid is much safer than sulfuric acid in terms of environmental impact, these findings can be used in a pharmaceutical industry setting to obtain a better, cleaner, and safer alternative to acetylsalicylic acid synthesis.

Keywords: acetylsalicylic acid, synthesis, green chemistry, medicinal chemistry

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INTRODUCTION

Acetylsalicylic acid (ASA) is an analgesic, antipyretic, antithrombotic, and anti-inflammatory drug that is widely used globally. It is administered orally in tablet form in different doses. Indications for the use of this medicine are short-term symptomatic relief of mild to moderate pain including headache, toothache, sore throat due to colds, menstrual pain, muscle and joint pain, back pain, mild arthritic pain and symptomatic pain relief, and fever reduction in colds and flu in doses of 500 mg. In a dose of 100 mg, it is used for the secondary prevention of myocardial infarction (MI) in patients with a history of acute coronary syndrome, for the secondary prevention of stroke in patients with a history of stroke, and the prevention of thromboembolism after operative or interventional procedures on blood vessels (1). ASA achieves its pharmacological effect by blocking cyclooxygenase 1 and 2 (COX 1 and COX 2), the enzymes responsible for the formation of prostaglandins, mediators of pain and inflammation. Originally, ASA was thought to be a prodrug of salicylic acid, but later it was found that the drug itself achieves a pharmacological effect (2). Salicylic acid and salicylates have been used in medicine for centuries. These are extracts obtained from the bark of white willow (Salix alba L.), from which this group of drugs got its name. ASA itself was first synthesized in 1897, and the synthesis was conducted by the famous German chemist, Felix Hoffmann (3). Today's ASA synthesis relies on the use of salicylic acid, acetic anhydride, and sulfuric acid (4). However, concentrated sulfuric acid is a strong and corrosive oxidizing agent that has the potential for serious adverse effects on the environment and human health. Such a synthesis is not entirely in accordance with the principles of green chemistry, which aims to reduce the use and generation of hazardous substances, as well as reduce the impact of chemicals on the environment. Concentrated sulfuric acid can cause severe burns, emit harmful gases when used and can pollute water and soil if disposed of improperly (5). Green chemistry, also known as sustainable chemistry or environmentally benign chemistry, is a field of chemistry that focuses on designing and developing chemical processes and products that minimize the use and generation of hazardous substances. It aims to promote the principles of sustainability, efficiency, and environmental responsibility in chemical manufacturing and related industries. The goal of green chemistry is to reduce or eliminate the use and production of hazardous substances, thereby minimizing the environmental and health impacts associated with traditional chemical processes (6). This involves the development of innovative methods and techniques that prioritize the use of renewable resources, the reduction of waste and energy consumption, and the prevention of pollution. The aim of this study is to provide a comparison of the synthesis of ASA, based on traditional and green chemistry synthesis and to compare the final yields of ASA.

MATERIALS AND METHODS

Materials

Salicylic acid (Semikem d.o.o., Sarajevo, Bosnia and Herzegovina), acetic anhydride (Kefo d.o.o., Istočno Sarajevo, Bosnia and Herzegovina), and concentrated sulfuric acid (MIKRO+POLO d.o.o., Sarajevo, Bosnia and Herzegovina) were used for the synthesis of ASA in the traditional approach. Salicylic acid (Semikem d.o.o.), acetic anhydride, and 85% phosphoric acid (Merck, Rahway, NJ, United States of America) were used for the synthesis of ASA, based on the principles of green chemistry. Universal indicator paper (pH 0 – 14) (KEFO d.o.o.) was used to determine the pH value of the solution. The mixture was heated on a water bath (Fisher Scientific, Waltham, MA, United States of America) and was filtered through a Büchnner funnel to which a water supply was connected. Purification of the final product was carried

out using a recrystallization process with ethyl acetate (Sigma-Aldrich, St. Louis, MO, United States of America). ASA standard (Agency for Medicines and Medical Devices of Bosnia and Herzegovina, Sarajevo, Bosnia and Herzegovina), acetonitrile (Kefo d.o.o.), ultrapure water (prepared in-house) and methanol (Semikem d.o.o.) were used to prove ASA composition. The determination of ASA was conducted using high-performance, thin-layer chromatography (HPLC) coupled to a UV-Vis spectrophotometer - Agilent 1100 (Agilent Technologies, Santa Clara, CA, United States of America) on an Agilent Zorbax SB C18 column (4.6 × 250 mm, 5 µm).

Methods

An amount of 3.0 g of salicylic acid was used for the synthesis of ASA by the traditional method: 3.0 g (21.7 mmol) of salicylic acid was transferred into a 50 mL round-bottomed flask and 7 mL (74.5 mmol) of acetic anhydride was added to the salicylic acid. The reaction mixture was stirred. After a few minutes, concentrated sulfuric acid was added dropwise to the reaction mixture until the reaction mixture reached a pH value of 6.0. The flask with the reaction mixture was then placed on a Liebig cooler with the thermostat in place. The flask with the reaction mixture was placed in a water bath and heated for 30 minutes at 50 °C. Subsequently, 60 mL of hot water was added to the reaction mixture, and the mixture was heated until the crystals dissolved. The mixture was then cooled, and the precipitated ASA crystals were filtered through a Büchnner funnel and washed several times with cold water. To remove the excess salicylic acid, a recrystallization process with ethyl acetate was performed (7). The synthesis procedure was repeated five times. For the synthesis of ASA using green chemistry methods, the same procedure was repeated. The only difference was that this process did not utilize concentrated sulfuric acid, but 85% phosphoric acid to achieve a pH value of 6.0 (8).

All samples were dried for 24 hours at room temperature. After drying, the samples were weighed, and the yield was calculated for all samples. After calculating the yield, ASA purity was determined by means of HPLC. A mixture of acetonitrile and water in a ratio of 25:75 (v/v) was used as the mobile phase. The pH of the mobile phase was adjusted to 2.5 with 85% phosphoric acid. The flow was set at 2.0 mL min-1 and the spectra were recorded at 207 nm. The duration of the method was set to 12 min. The standard sample of ASA was dissolved in methanol to a final concentration of 200 µM. The retention time for ASA was determined to be 7.88 min (9).

Statistical analysis

Syntheses of ASA using the traditional method and the principles of green chemistry were repeated five times. Theoretical and experimental yields were calculated for both types of syntheses. The Kolmogorov-Smirnov test was used to test the normality of the data distribution and normal distribution was confirmed. In order to determine the existence of a statistically significant difference between the average values of ASA utilization, obtained by traditional synthesis as well as synthesis based on green chemistry, a t-test was used. The p-value, confidence interval, and standard error were calculated. If the p-value was greater than 0.05, it was considered that there was no statistically significant difference between the two observed samples.

RESULTS

The acetylation reaction of salicylic acid with acetic anhydride, which produces ASA and acetic acid, is shown in Figure 1. Concentrated sulfuric acid was used for the synthesis of ASA using the traditional approach, and 85% phosphoric acid was used for the synthesis of ASA based on the principle of green chemistry.

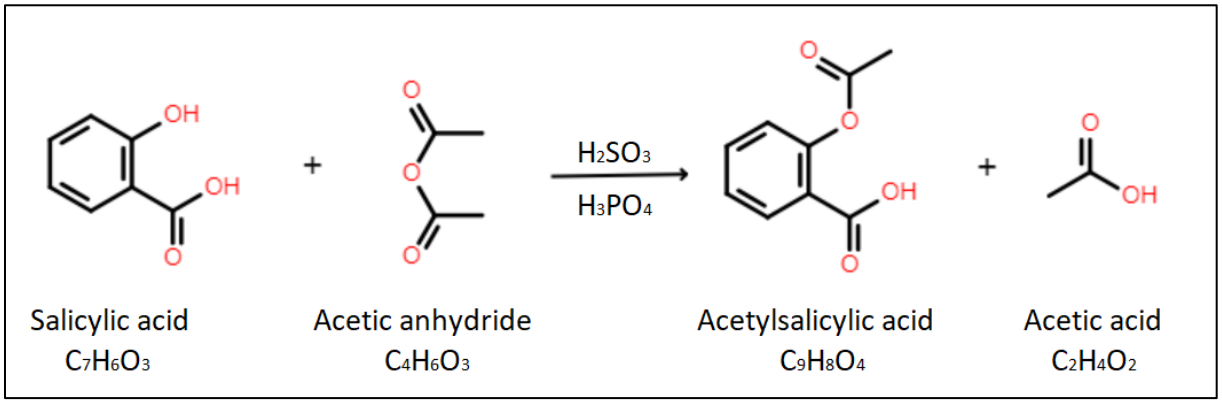

Figure 1. ASA synthesis reaction

Salicylic acid was determined to be the limiting reagent in this chemical reaction. The maximum yield of ASA in the reaction shown above was calculated as 3.896 g. The syntheses and yields using the traditional approach are shown in Table 1.

Table 1. Yields of ASA using the traditional synthesis process

Synthesis	Mass (g)	Theoretical yield (g)	Experimental yield (%)
1	3.011		77.4
2	3.182		81.6
3	3.229	3.896	82.8
4	3.089		79.2
5	3.053		78.3
$\bar{x}$	3.113		79.8
$\tilde{x}$	3.089		79.2
SD	0.091		2.269

$\bar{x}$ – mean; $\tilde{x}$ – median; SD – standard deviation.

During the synthesis of ASA using the traditional approach, an average of 3.113 g of ASA was obtained. This represents a yield of 79.8%. The highest yield was observed in synthesis 3 (3.229 g; 82.8%), and the lowest yield was observed in synthesis 1 (3.011 g; 77.4%). The syntheses and yields of ASA based on the principles of green chemistry are shown in Table 2.

Table 2. Yields of ASA using the green chemistry synthesis process

Synthesis	Mass (g)	Theoretical yield (g)	Experimental yield (%)
1	2.998		76.9
2	3.065		78.6
3	3.155	3.896	80.9
4	3.201		82.2
5	3.101		79.5
$\bar{x}$	3.104		79.6
$\tilde{x}$	3.101		79.5
SD	0.071		1.831

$\bar{x}$ – mean; $\tilde{x}$ – median; SD – standard deviation.

Table 3. Statistical analysis of both approaches

Parameters	Traditional approach	Green chemistry
Mean	3.089	3.101
Standard deviation	0.091	0.071
Sample size	5	5
Difference	0.012	
Standard error	0.052	
95% confidence interval	from -0.1070 to 0.1310	
Significance level (*p*)	0.8220	

**t-test was used*

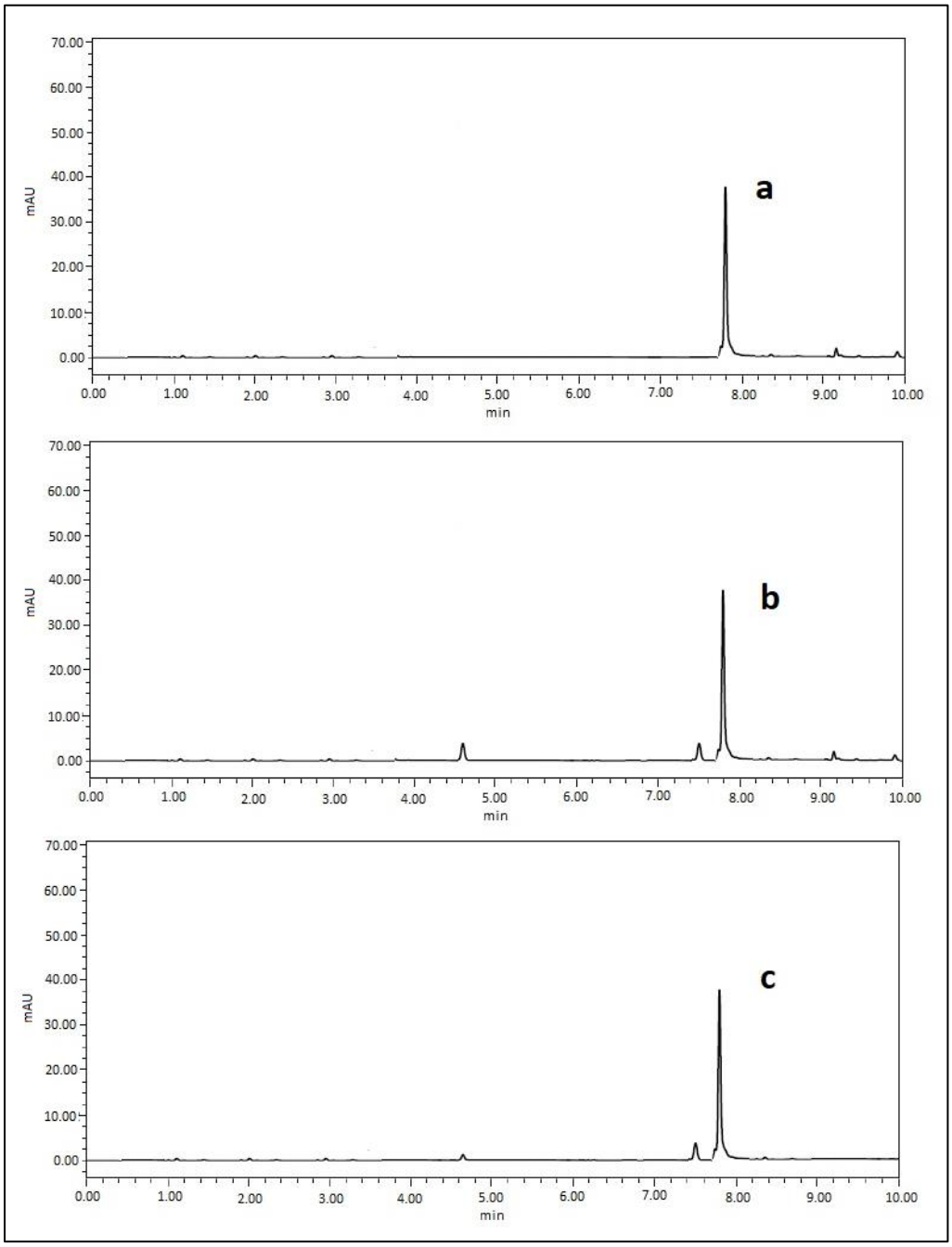

Figure 2. HPLC analysis of the ASA standard (a), traditionally obtained ASA (b) and green chemistry obtained ASA (c)

During the synthesis of ASA based on the principles of green chemistry, an average of 3.104 g of ASA was obtained. This represents a utilization of 79.6%. The highest yield was observed in synthesis 4 (3.201 g; 82.2 %), and the lowest yield was observed in synthesis 1 (2.998 g; 76.9 %). Statistical data analysis is shown in Table 3.

Between the observed mean values of both ASA synthesis approaches, no statistically significant difference was observed in the obtained ASA masses (p=0.8220). All samples were subjected to the HPLC proofing process according to the previously described principles (Figure 2).

All observed samples showed the same retention time at approximately 7.8 minutes. Certain signals shown elsewhere on the chromatogram can be interpreted as impurities or residual parts of salicylic acid, which is the main contaminant of ASA (10). The appearance of ASA after drying is shown in Figure 3.

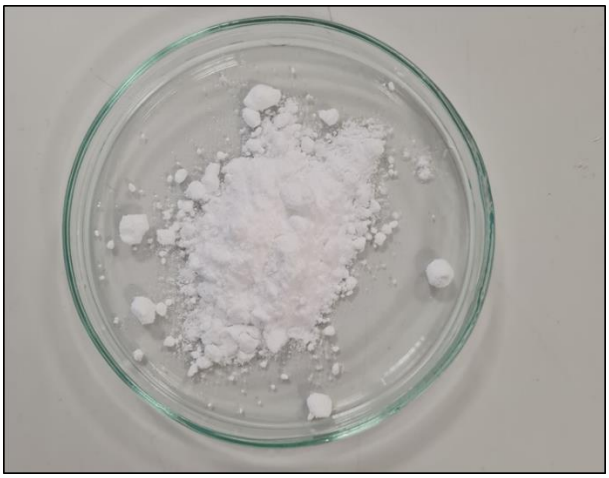

Figure 3. ASA product after drying

After the completion of the synthesis process, the product was obtained in the form of colorless, small, needle-like, white crystals. The product has a barely perceptible smell of acetic acid and a slightly sour taste. The product was easily soluble in ethanol, moderately soluble in ether and chloroform, and hardly soluble in cold water. The melting point was determined to be 135 °C.

DISCUSSION

As people's awareness of man's ecological footprint on Earth increases, the principles of environmental protection and sustainable development have also increased in importance. This is also the case with the pharmaceutical industry, an industry that can have a negative effect on the environment. Traditional chemical processes and products in the pharmaceutical industry can be a source of significant air, water, and soil pollution. The application of green chemistry helps to reduce the emissions of harmful substances, reduces the consumption of energy and raw materials, and reduces the amount of waste that pollutes the environment. This helps preserve natural resources, sustain ecosystems, and protect endangered species. In this experiment, we present the results of the synthesis of ASA - one of the most used drugs in the world - based on the principles of green chemistry. Using a very simple synthesis process, the procedure changes only in the step that uses a reagent to acidify the medium in which the pharmaceutical synthesis is carried out. The traditional approach in this step involves the application of concentrated sulfuric acid. The use of sulfuric acid can lead to various types of environmental pollution, such as corrosion of materials, a negative impact on living organisms, danger to human health, and a negative impact on atmospheric processes (11, 12). As an example, the Australian Government's Department of Climate Change, Energy, the Environment and Water states that the main contributors of sulfuric acid emissions are the industrial sectors involved in the manufacturing and utilization of sulfuric

acid. Industries such as metal smelters, phosphate fertilizer producers, oil refineries, chemical manufacturers, battery manufacturers, producers of fabricated metal products, manufacturers of electronic components, and manufacturers of measuring and controlling devices utilize sulfuric acid in their production processes. Typically, these emissions are released into the atmosphere, unless there is an accidental spill that leads to the contamination of water or land. In such cases, the spilled sulfuric acid can also contribute to emissions in the form of air pollution (13). The Canadian Government classifies sulfuric acid as one of the national pollutants, providing maps and guidelines on the safe disposal and transfer of this chemical (14).

As ASA is one of the most used and therefore synthesized drugs in the world and bearing in mind that most pharmaceutical companies use the traditional synthesis of ASA, the environmental effect of sulfuric acid used in this industry is significant. Therefore, in this paper, we provide a safer and green chemistry-friendly alternative to the ASA synthesis. This alternative uses phosphoric acid instead of sulfuric acid. Phosphoric acid is less toxic, less corrosive, has less impact on air pollution, and has a lesser impact on the environment by comparison with sulfuric acid (15). Moreover, the price of phosphoric acid is approximately the same as the price of sulfuric acid. In this paper, we showed that there is no statistically significant difference in the yields of ASA obtained by synthesis using sulfuric acid vs phosphoric acid. Moreover, the duration of the synthesis was the same and the product quality was consistent, as confirmed with HPLC. However, our study has some limitations. These limitations may include specific ASA production methods, the acid concentrations used, the reaction conditions, and the environmental conditions. All of these parameters severely affect the ASA production process. Therefore, general conclusions can only be applied within these frameworks. However, we strongly believe that the findings of this study are critical for the future development of the pharmaceutical industry and the sustainability of environmental practices, as they pertain to drug production. We recommend that biomedical scientists be aware of the findings of this study, as they can significantly impact the future outcomes of their work in pharmaceutical industry settings.

CONCLUSION

Based on the results of this study, it can be concluded that ASA can be synthesized using phosphoric acid instead of sulfuric acid. There is no statistically significant difference in the obtained yields of ASA, based on the traditional approach and the green chemistry approach. As phosphoric acid is much safer than sulfuric acid in terms of environmental impact, corrosiveness, and human health impact, these findings can be used in a pharmaceutical industry setting to obtain a better, cleaner, and safer alternative to ASA synthesis.

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CONFLICT OF INTEREST
Author LG declares that she has no conflict of interest; author MK declares that he has no conflict of interest.

AUTHORS' CONTRIBUTIONS
LG: acquisition of data, literature review, contribution to study conception and design; MK: contribution to study conception and design, literature review, supervision, interpretation of data, critical revision of the paper.

ETHICAL BACKGROUND

Institutional Review Board statement: The study was conducted according to the guidelines of the Declaration of Helsinki and approved by the Ethics Committee.

Informed consent statement: NA.

Data availability statement: We deny any restrictions on the availability of data, materials, and associated protocols.

Derived data supporting the findings of this study are available from the corresponding author on request.

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