International Science and Technology Journal
المجلة الدولية للعلوم والتقنية
Volume 37 العدد
Part 1 المجلد
المجلة الدولية للعلوم والتقنية
International Science and Technology Journal
ISTJ

http://www.doi.org/10.62341/faff0915

Received	**2025/08/20**	**تم استلام الورقة العلمية في**
Accepted	**2025/09/13**	**تم قبول الورقة العلمية في**
Published	**2025/09/15**	**تم نشر الورقة العلمية في**

A green Method for Synthesizing Aspirin Using Microwave Radiation and Its Comparison with the Conventional Method

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Abstract:
Aspirin is a nonsteroidal anti-inflammatory drug (NSAID) that functions similarly to other NSAIDs but also inhibits the normal activity of platelets. It is the most widely produced and sold medication worldwide. This study aimed to produce aspirin in an environmentally friendly way and compare it to the traditional method. Aspirin is typically manufactured using acetic anhydride and salicylic acid. The process involves reacting salicylic acid with acetic anhydride in the presence of a catalyst (such as phosphoric acid or sulfuric acid) or without a catalyst, following environmentally friendly and traditional methods. Aspirin production is carried out through a series of carefully controlled steps. Conventional heating requires 25-30 minutes at 60 °C to synthesize aspirin, while microwave techniques achieve comparable or higher yields with shorter reaction times (5-8 minutes at 175 W). The yield of aspirin using microwaves with a catalyst was 92%, whereas without a catalyst, it was 82%, compared to 76% with the conventional method. From these results, we conclude that microwave synthesis reduces time consumption and produces a higher purity, better-quality product. We recommend conducting more extensive studies using the microwave method on aspirin and other compounds.

Keywords: aspirin, synthesis, salicylic acid, acetic anhydride, acetylsalicylic acid

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طريقة خضراء لاصطناع الأسبرين باستخدام إشعاع الميكروويف ومقارنتها بالطريقة التقليدية

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الملخص:

الأسبرين أحد الأدوية المضادة للالتهابات غير الستيرويدية (NSAIDs)، حيث يعمل بآلية مشابهة لبقية هذه المجموعة الدوائية، إضافةً إلى تثبيطه للنشاط الطبيعي للصفيحات الدموية، ويُعَدّ الدواء الأكثر إنتاجًا وتداولًا على مستوى العالم. وهدفت هذه الدراسة إلى إنتاج الأسبرين بطريقة صديقة للبيئة ومقارنتها بالطريقة التقليدية. حيث تم تحضير الأسبرين عادةً من أنهيدريد الأسيتيك وحمض الساليسيليك، حيث تتفاعل مادة حمض الساليسيليك مع أنهيدريد الأسيتيك بوجود محفز (مثل حمض الفوسفوريك أو حمض الكبريتيك) أو في غياب المحفز وذلك باستخدام الطرق التقليدية أو الصديقة للبيئة. تمر عملية التحضير بعدة خطوات مضبوطة بعناية إذ يتطلب التسخين التقليدي مدة تتراوح بين 25–30 دقيقة عند درجة حرارة 60 °م لإتمام التفاعل في حين تتيح تقنية الموجات الميكروويفية الحصول على نتائج مماثلة أو مردود أعلى في وقت أقصر (5–8 دقائق عند قدرة 175 واط). حيث بلغت نسبة إنتاج الأسبرين باستخدام الموجات الميكروويفية مع محفز 92% وبدون محفز 82% مقارنةً بـ 76% عند استخدام الطريقة التقليدية. ومن هذه النتائج نستنتج أن التخليق باستخدام اشعاع الميكروويف يقلل من الزمن المستغرق، وينتج منتجًا أعلى نقاءً وجودة. ونوصي بأجراء دراسات أوسع باستخدام طريقة الميكروويف على الأسبيرين ومركبات اخري.

الكلمات المفتاحية: الأسبرين، التحضير، حمض الساليسيليك، أنهيدريد الأسيتيك، حمض أسيتيل الساليسيليك

Introduction:

In organic chemistry, many traditional synthesis processes require several hours under conventional heating conditions. However, microwave-assisted synthesis significantly reduces reaction times, often to a fraction of the original duration, while improving yields

http://www.doi.org/10.62341/faff0915

and product quality. Microwaves generate oscillating magnetic fields that induce rotation of polar molecules, enhancing molecular collisions and thus accelerating reaction rates (Kappe, 2004).

Aspirin is one of the most widely used medications globally, with an estimated annual consumption of 40,000 to 44,000 tons (Kazi *et al.,* 2024; Patil et al., 2024). It is listed on the World Health Organization's Essential Medicines List and is available as a generic drug (WHO, 2023). In 2017, aspirin ranked as the 42nd most commonly prescribed medication in the United States, with over 17 million prescriptions dispensed (CDC, 2018).

Aspirin is primarily used as a pain reliever and also reduces blood clot formation in arteries, thereby lowering the risk of heart attacks (Patil *et al.,* 2024). Its synthesis involves an acylation reaction, where the hydroxyl group of salicylic acid attacks the carbonyl group of acetic anhydrides (Kazi *et al.,* 2024).

This synthesis method aligns with the principles of green chemistry, which focus on manufacturing chemical products and processes that minimize or eliminate the use or generation of hazardous substances harmful to human health and the environment. The U.S. Environmental Protection Agency defines green chemistry as a set of principles aimed at reducing or eliminating hazardous substances in chemical design and manufacture (Environmental Protection Agency, 2020).

There are many Reaction types and substance classes in organic chemistry, and many manufacturing processes require half an hour to an hour of heating at room temperature for this type of reaction, but this reaction can be completed in minutes with higher efficiency and yield. Using microwaves creates an oscillating electromagnetic field, which enhances molecular interactions. (Anastas and Warner, 1998).

A microwave oven operates at a frequency of 2,500 megahertz. In one second, a microwave oven at this frequency reverses the direction of the electromagnetic field 2,500,000,000 times. Therefore, microwave irradiation provides very high thermal efficiency (Anastas, and Williamson, 1998).

This study aimed to produce aspirin in an environmentally friendly way and compare it to the traditional method.

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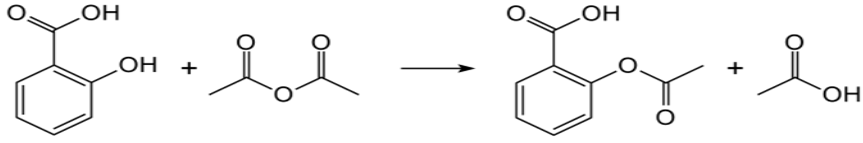
Materials and Methods

•Chemical use:

Salicylic acid- Acetic acid anhydride- Concentrated sulfuric acid- Ice water- distilled water - Iron chloride (|||).

•Reaction equation:

To produce acetyl salicylate (aspirin) according to the following equation figure (1):



(138.1g/mol) (120.1g/mol) (180.1g/mol) (60.1g/mol)

Fig. (1): O-Acetylation of salicylic acid to give acetyl salicylate (aspirin)

• Preparing Aspirin Using a Microwave:

- **Experiment Steps:**

Two g of salicylic acid was weighed and transferred to a 125 ml conical flask, then 4 ml of acetic acid anhydride was added to the conical flask, and the reaction mixture was microwaved for 6 minutes. The completion of the reaction was checked using the ferric chloride (|||) test (about 10 mg of the substance was dissolved in about 5 ml of ethanol, and 1 to 2 drops of 0.1 M aqueous iron (III) chloride solution were added. The appearance of intense violet color in the solution indicated the presence of salicylic acid.) After this test, 5 mL of ice water was added to the reaction mixture, and aspirin precipitated. And we cooled it in a water bath for 5 minutes and heated it in the microwave for another minute. Then I filtered it using a Buchner funnel. After the filtration process was completed, we obtained the aspirin, dried it, and weighed it.

• Preparing aspirin by the traditional way:

Two grams of salicylic acid were weighed using a sensitive balance and transferred to a 125 ml conical flask. Then, 4 mL of acetic acid anhydride was added to obtain the reaction mixture. 5 drops of concentrated sulfuric acid were added, and the mixture was stirred well. Then it was placed in a hot water bath until boiling for 25 minutes. The reaction mixture was placed in a cold-water bath, and crystallized aspirin was obtained. Then it was stirred using a glass rod, and the completion of the reaction was checked using the ferric chloride test (|||). After performing this test, 5 mL of ice water

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was added to the reaction mixture, and the aspirin precipitated and filtered. It was recrystallized and weighed.

• Recrystallization of Aspirin:

About 5 mL of ethanol was added to the crystals. The solution was heated in a hot water bath. 15 ml of warm water was added to the alcohol solution. The beaker was covered with a watch glass and left aside to cool. (The crystallization process can be accelerated by placing the beaker in an ice bath.) It was left to stand for some time until the crystals crystallized from the solution, then the crystals were filtered and dried.

The efficiency of the chemical reaction and the techniques used to obtain the compound can be calculated from the ratio of the actual yield to the

theoretical yield, to give the percentage yield.

yield % = amount of product recovered / Theoretical amount of product X 100

• Results and Discussion:

Based on experimental calculations in Table (1), it was observed that the amount of aspirin produced using microwave irradiation was higher than that obtained through the conventional method. Additionally, the product synthesized via microwave heating exhibited greater purity. Interestingly, the use of a catalyst in the microwave-assisted synthesis resulted in a longer reaction time and lower production rate compared to the catalyst-free process. The overall time required to prepare the aspirin sample using microwave irradiation was remarkably short (6 minutes) compared to the traditional method, which took about 25 minutes. Moreover, the microwave method yielded a high-purity product with a 93% yield, achieved without using any solvent. These findings are consistent with the results reported by (Patil, *et al.*, 2024), where aspirin was prepared in 7 minutes with a similar yield of 92% figure (2).

TABLE (1): shows a Comparison of Reaction Times and Yield in Aspirin Synthesis Using Microwave Irradiation and Conventional Heating

	Synthesis of aspirin using microwave irradiation			**Synthesis of aspirin with conventional heating.**	
Catalyst	H_3po_4	H_2SO_4	Non	H_2SO_4	H_3po_4
Reaction time (min)	6	6	6	25	30
Yield (%)	90	88	93	76	82

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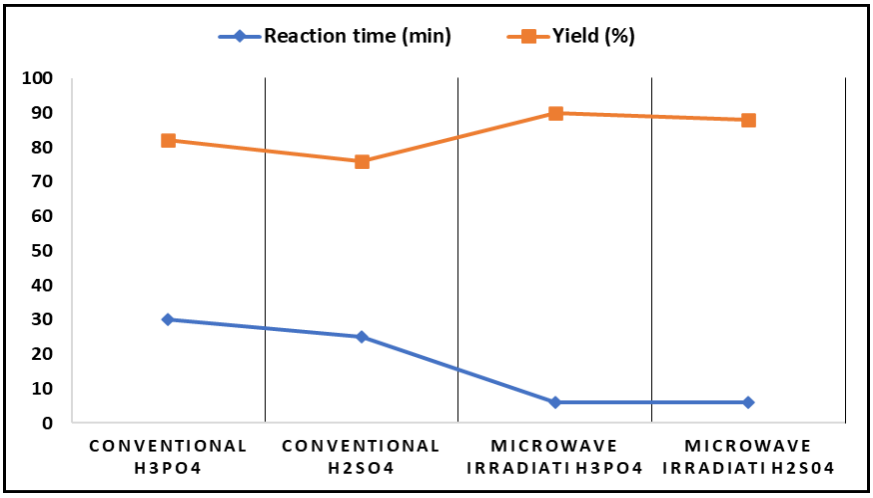

Fig. (2): shows a Comparison of Microwave Irradiation and Conventional Heating

These outcomes are further supported by the study of (Kazi, *et al.* 2024), who synthesized aspirin and its derivatives using microwave heating at 175 watts for 3–7 minutes. They achieved an 81.6% yield of pure aspirin without any solvent. The study demonstrated that microwave-assisted synthesis was more efficient than the conventional method, which required 30 minutes at 55 °C. Their findings also emphasized the eco-friendly nature of the technique and its ability to produce high-purity products in significantly less time.

These results align well with prior literature in the field. For example, Kappe (2004) highlighted that microwave-assisted organic synthesis (MAOS) enhances reaction rates, increases yields, and improves purity due to efficient internal heating and uniform energy distribution. Similarly, Varma 1999) emphasized the benefits of solvent-free microwave synthesis in producing pharmaceutical compounds, including aspirin analogs. Caddick (1995) reviewed a wide range of organic reactions, showing that microwave irradiation drastically reduces reaction times compared to conventional heating. Furthermore, Loupy *et al.* (1998) reported substantial improvements in yields and purity across many organic reactions utilizing microwave energy, also noting the sustainability of the process.

Physical and Chemical Properties of the obtained aspirin were observed in Table (2).

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TABLE (2): shows the physical properties of the obtained aspirin.

Color	White
Appearance	Crystalline-Powder
Solubility	Soluble in water
Odour	Odourless
State	Solid
Flame Test	Positive
Melting point	138 - 142
Poling point	140 - 141 C^0

The studied compound appeared as a white crystalline powder, indicating a high degree of purity and a well-organized internal molecular structure, as crystalline forms generally suggest a regular arrangement of molecules (Zhou and Liu, 2016). The compound was found to be soluble in water, suggesting the presence of polar functional groups capable of forming hydrogen bonds with water molecules, which enhances its potential applications in aqueous environments (Morrison and Boyd, 2010**;** Clayden *et al.*, 2012).
Moreover, the compound was odorless, indicating the absence of volatile or strongly odorous functional groups such as thiols or low molecular weight amines. This property is desirable in pharmaceutical and industrial applications where minimizing unpleasant odors is beneficial for safety and user acceptability. The solid state at room temperature suggests good thermal and physical stability, facilitating safe storage and handling procedures (Meyers, 2007; Dean, 2015).
A positive flame test result indicates the presence of metal ions in the compound. Flame tests are simple and effective methods for identifying metallic elements based on the characteristic color emitted during combustion (Atkins and de Paula, 2014).
The melting point range was recorded between 138°C and 142°C, a relatively narrow range that indicates the compound's purity, as impurities tend to lower and broaden melting point ranges (Pavia *et al.*, 2014).

The poling point was measured between 140°C and 141°C, closely aligning with the melting point and confirming the compound's crystalline stability and the accuracy of the measurements (Vogel, 2013).

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Conclusion:

The current study demonstrated that microwave-assisted aspirin synthesis is more efficient than the conventional method. The product appeared as a stable, white, odorless, water-soluble crystalline powder with a steep melting point, confirming its purity. The advantages of using microwave irradiation, including shorter reaction times, higher yields, higher purity, and environmental friendliness, are highlighted here, making it a superior method for aspirin synthesis.

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