Experimed 2022; 12(1): 12-7

ORIGINAL ARTICLE

DOI: 10.26650/experimed.2022.1068934

Synthesis of Natural Salicylic Acid as a Cosmetic Ingredient Using Green Chemistry Methods

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Cite this article as: Ozokan G, Sagir T, Emekli-Alturfan E. Synthesis of natural salicylic acid as a cosmetic ingredient using green chemistry methods. Experimed 2022; 12(1): 12-7.

ABSTRACT

Objective: Salicylic acid (SA) is a keratinolytic agent also used as preservative in cosmetic products. Green chemistry, known as sustainable chemistry, is the design of products and processes eliminating the use of chemicals. It is applicable throughout a chemical product's life cycle, including its design, manufacture, use, and final disposal. The aim of this study was to synthesize SA with green chemistry methods using different amounts of wintergreen oil and to optimize the relevant steps in this path.

Materials and Methods: The SA was synthesized from natural wintergreen oil using green chemistry methods. First laboratory-scale synthesis was developed and 15 laboratory-scale synthesis trial patterns, using reaction temperature, wintergreen oil-sodium hydroxide molar ratio, sodium hydroxide-water weight ratio, reaction time and pH were performed. Purity was analysed with gas chromatography-mass spectrometry (GC-MS) and moisture analysis was performed.

Results and Conclusion: As a result of pilot production run with 1 kg, 5 kg, and three batches of 20 kg of wintergreen oil, SA was produced with a yield range of 91.06-93.92 %. The resulting SA batches had a purity of approximately 99%. This is a sufficient degree of purity for SA to be used as a raw material in cosmetics products. Filtering the SA solution using a filter press reduced crystal drying time and brought down the total production time to eight days.

Keywords: Salicylic acid, green chemistry, wintergreen oil, cosmetic

INTRODUCTION

Salicylic acid (SA) is a beta-hydroxy acid, and its name originates from the Latin word salix, which means "willow tree." As an ingredient in Aspirin, SA has numerous health benefits. It has a therapeutic effect on various skin conditions, such as acne and eczema (1). It is used in the production of cosmetic care products, such as creams, masks, shampoos and tonics (2). Moreover, SA has an exfoliating effect on skin, which helps to remove dead cells (3).

As a raw material, it is used in the production of food and textiles, as well as pharmaceuticals and cosmetic products (4). Although it has been widely used in cosmetic products in recent years due to its protective properties and dermatological effects, the SA contained in these products has been produced via industrial synthesis. In this method, phenol (which is a highly toxic chemical) is used as a raw material. The synthesis reaction of SA is presented in Figure 1. Industrial SA synthesis creates certain impurities in the end product which have toxic effects as indicated in the pharmacopeia. In contrast, the natural synthesis method uses the oil of wintergreen, which has a methyl salicylate

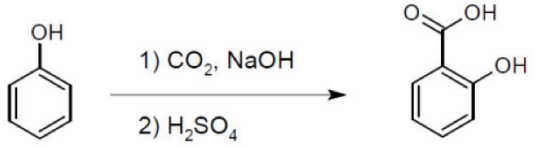

Figure 1. Industrial synthesis of SA.

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Submitted: 07.02.2022 **Revision Requested:** 02.03.2022 **Last Revision Received:** 31.03.2022 **Accepted:** 31.03.2022

content of over 99%. Oil of wintergreen is first hydrolysed with sodium hydroxide and then further hydrolysed with hydrochloric acid to obtain crystal SA free from toxic impurities (5).

SA and its derivatives have long been recognized as important pharmacological agents. Salicin, the active ingredient in willow bark, was isolated in 1828. Hippocrates, the father of medicine, prescribed willow bark to reduce fever and pain during childbirth in the fifth century B.C. Salicylate levels have been found to be high in a variety of plant species other than willow. Another medicinal derivative known as wintergreen oil also contains methyl salicylate. Medicinal plants high in salicylates have been used by various cultures around the world for thousands of years and continue to be used today (6).

Chemical peeling is a technique used to improve, smooth, and revitalize the skin through controlled removal of epidermis/dermis, enabling healthy skin formation (7). The aim of chemical peeling is to cause damage to skin layers up to the desired depth, in order to treat various skin lesions and conditions by leveraging the increased collagen and elastin production triggered by wound healing (8). The most common chemical peeling agents are alpha-hydroxy acids (AHA) (lactic acid, glycolic acid, and fruit acids), trichloroacetic acid (TCA), beta-hydroxy acids (BHA, SA), Jessner solution, and their combinations (9). SA affects the epidermis and is generally used in the treatment of acne, acne scars, blackheads, and photo-aging, as well as in the secondary treatment of skin spots. It penetrates into the pores of the skin, preventing sebum build-up and balancing skin tone. Marczyk et al. compared the effects of 50% pyruvic acid and 30% SA peels on skin lipids and found that SA had a greater sebumetric impact than pyruvic acid (10). In the 1860s, it was discovered that SA could soften and exfoliate the stratum corneum. With its comedolytic properties, SA works to dissolve dead skin cells, and has an anti-inflammatory effect in lower concentrations, which helps to treat acne and reduce acne scars (11). SA is also a desmolytic agent because it disrupts cellular junctions rather than breaking intercellular keratin filaments (12). Imayama et al. concluded that peeling with SA can cause changes in the underlying dermal tissue without directly wounding the skin (13, 14). Its anti-inflammatory and anti-irritant properties enable SA to be well-tolerated by all skin types (15). It also soothes painful acne and sensitive skin (16).

Acne vulgaris is a common condition that can cause both physical and psychological problems, such as redness after acne, hyperpigmentation after inflammation, acne scars, and affects the quality of life. SA acts on normal keratinization, reduces inflammation, and regulates sebum production with a comedolytic action. The SA concentration used to treat acne is 0.5–5% (17). SA has been shown to reduce the lipid content of the sebocytes cell line (SEB-1) to suppress the inflammatory response in SEB-1 by inhibiting the NF-kB pathway (16). SA is also effective in the treatment of dandruff, caused by keratinocyte hyper-proliferation as it loosens the bonds between the corneocytes, allowing them to be washed away (18, 19).

Green chemistry is a novel method in chemistry that aims to minimize the environmental impact during the production and use of chemicals (20). It is based on ecological concerns and takes into account economic and technological factors. It favours the most ecologically-economically advantageous solution of existing alternatives (21).

The foundation of this philosophy was laid with the enactment of the Environmental Protection Act in the United States (US) in 1990. This act focused on the prevention of polluting waste and was followed by the establishment of the Office of Pollution Prevention and Toxics within US Environmental Protection Agency (EPA) (22). The twelve green chemistry principles were presented as the first guidebook on green chemistry by Anastas, a US EPA representative, and Warner (23). The history of green chemistry was initiated by the pollution prevention movement in 1990. Then it was formalized with the establishment of EPA in 1991"Presidential Green Chemistry" awards were given for the first time in 1996. The "Green Chemistry and Engineering" conference was first held in 1997 (24).

The goals of green chemistry are schematized in Figure 2. To achieve these goals, the principles of green chemistry include preventing waste, maintaining atom economy and synthesis of less toxic chemicals, and developing safer chemicals, safer solvents, and auxiliaries. Energy efficiency should also be maintained through the use of renewable feedstocks. Derivatization is aimed to be reduced, minimized, or avoided, as these steps require additional reagents and can cause waste. Chemical products should be designed so that when they reach the end of their useful life, they degrade into harmless degradation products and do not persist in the environment. Analytical methodologies that enable real-time, in-process monitoring and control prior to the formation of hazardous substances must be developed further. Finally substances used in a chemical process should be selected to reduce the likelihood of chemical accidents such as releases, explosions, and fires (24, 25).

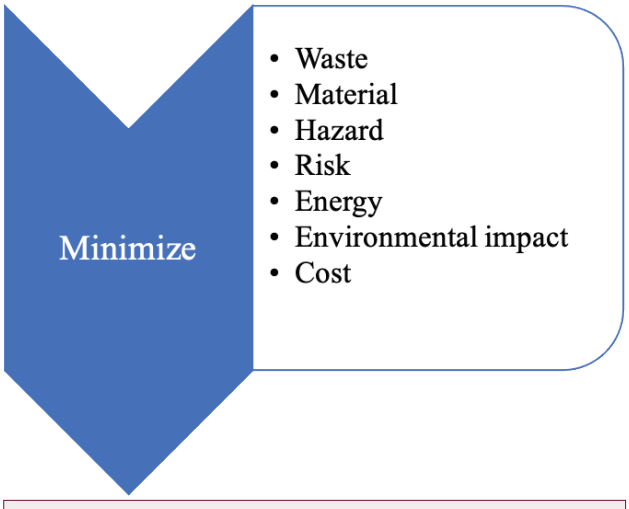

Figure 2. Goals of green chemistry.

In the light of this information, the aim of our study was to synthesize SA with green chemistry methods using different amounts of wintergreen oil and to optimize the relevant steps in this path.

MATERIALS AND METHODS

Salicylic Acid Synthesis using Green Chemistry

Developing Laboratory-Scale Synthesis

SA was synthesized from natural wintergreen oil using organic synthesis and green chemistry methods. First, sodium salicylate was synthesized and then it is crystallized as described below. The main synthesis steps were schematized in Figure 3.

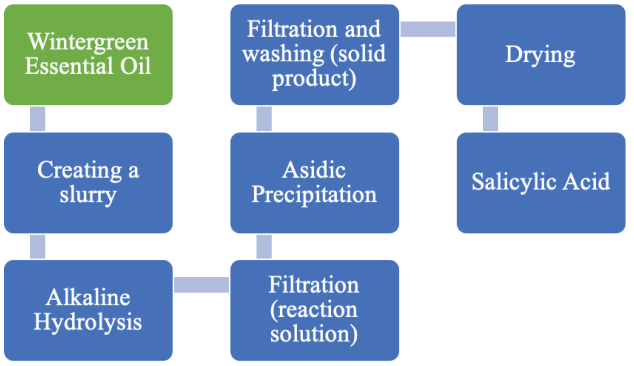

Figure 3. The main steps of SA synthesis.

Sodium Salicylate Synthesis

Sodium hydroxide solution (5M) was slowly added to wintergreen oil over 10-15 minutes. White precipitates formed. Reflux was commenced by turning on the heater and stirrer. A homogeneous solution was formed within one hour; heating continued for a further two hours for three hours of total reflux. After three hours, the solution was left to cool at room temperature. The reflux equipment system is shown in Figure 4.

Crystallization of Salicylic Acid

At room temperature, to the reaction solution the HCl solution (6M) was slowly added over 30 minutes to reduce its pH to between 2 and 1.5. The addition of HCl created an exothermic reaction. The solution was cooled continuously while the HCl was added. The solution was left overnight to allow precipitates to

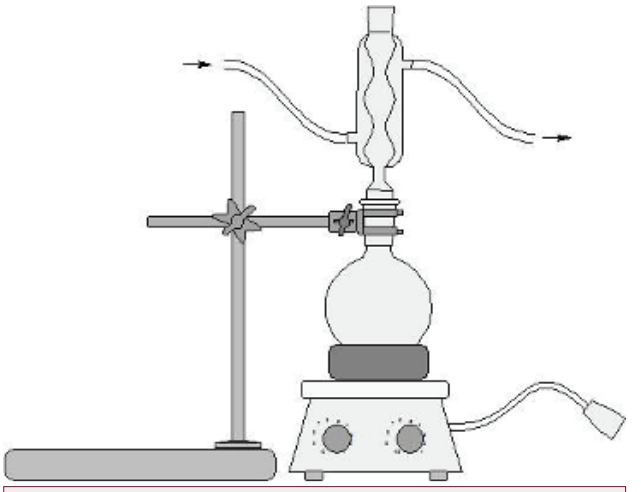

Figure 4. Reflux equipment system.

form. Then it was washed and filtered under vacuum. The crystals were washed using water and dried at 40°C for 3-4 days. The filtration equipment is shown in Figure 5 (26, 27).

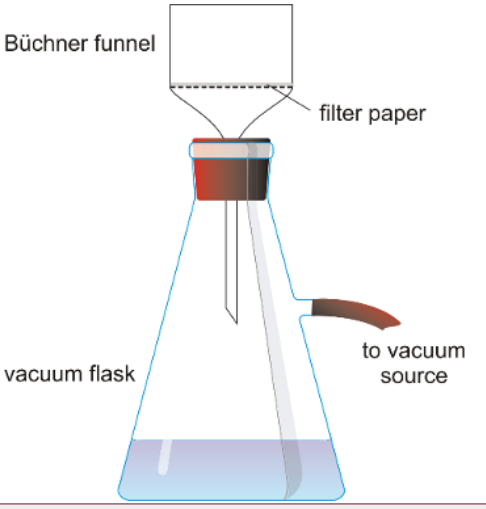

Figure 5. Filtration equipment.

Laboratory-Scale Synthesis Trial Pattern

In our studies a total of 15 trials were made, using the parameters in Table 1. The optimum parameters with the highest reac-

Table 1. Laboratory-Scale Synthesis Trial Pattern of SA.

Parameter 1	Reaction Temperature	80°C, 90°C, 100°C
Parameter 2	Wintergreen oil-sodium hydroxide molar ratio	1:3, 1:5, 1:7
Parameter 3	Sodium hydroxide-water weight ratio	1:5, 1:7, 1:10
Parameter 4	Reaction Time	2 hours, 3 hours, 4 hours
Parameter 5	pH (HCl precipitation)	1.5, 1.7, 2.0

tion yield were reaction temperature: 90°C; 1:7 wintergreen oil-sodium hydroxide molar ratio; 1:5 sodium hydroxide - water weight ratio; reaction time of 3 hours, and pH of 1.5. The resulting SA was analysed for purity using gas chromatography-mass spectrometry (GC-MS), which revealed a purity of 99%.

GC-MS Analysis

For the GC-MS analysis a HP-5ms ultra inert, 30 m x 250 µm x 0.25 µm column was used. Temperature program was arranged as follows: beginning: 60°C, final 260°C, and the temperature increase rate was 3°C per minute. Inlet temperature was 250°C and the MS detector temperature was 230°C. Analysis duration was 66.6 minutes. Helium flow rate and the split ratio were 1.1 ml/minute and 20:1, respectively.

Sample Preparation

5 mg of SA was dissolved in 1.5 ml of methanol. Injection volume was 1µl and SA retention time was 20.3 minutes. SA MS peaks were determined as 138, 120, 92, 64, 53 in molecular weight.

Moisture Analysis

The samples were placed in moisture analyser at 95°C, and it was observed that samples that were dried at 40°C for four days had a moisture content of under 0.5%.

Pilot-Scale Synthesis Optimization

Pilot-scale production was optimized by gradually increasing wintergreen oil amounts (1 kg, 5 kg, 20 kg). Synthesis parameters (caustic ratio, acid amount, drying time) were taken into account to obtain laboratory-scale synthesis data. Yield and impurity analyses were performed after each batch. The Pilot-Scale synthesis trial pattern of SA is given in Table 2.

Yield and Purity Analysis Criteria for Pilot-Scale Salicylic Acid Production

The criteria include the fulfilment of the following criteria: a yield of a minimum 80% raw material input, a minimum 95% purity as analysed by GC-MS and a maximum loss of 0.5 % on drying analysis through moisture analyser.

RESULTS

Results of Salicylic Acid Synthesis from 1 kg of Wintergreen Oil

At the end of sodium salicylate synthesis and crystallization steps, the product was dried for 14 days at 40°C to obtain 0.84 kg of SA with a yield of 92.47%. The resulting SA was analysed for purity using GC-MS, which revealed a purity of 98.25%. The product's moisture content was analysed at 95°C, showing that samples that were dried at 40°C for 14 days had a moisture content of under 0.5%.

Results of Salicylic Acid Synthesis from 5 kg of Wintergreen Oil

4.18 kg of SA with a yield of 91.96% was obtained. The resulting SA was analysed for purity using GC-MS, which revealed a purity of 97.95%. Moisture analysis revealed that samples dried at 45°C for 10 days had a moisture content of under 0.5%.

Results of Salicylic Acid Synthesis from 20 kg of Wintergreen Oil (20 kg batch)

For the first batch, 17.07 kg of SA with a yield of 93.92% was obtained. The resulting SA was analysed for purity using GC-MS, which revealed a purity of 99.16%. The product's moisture content was analysed at 95°C, showing that samples that were dried at 50°C for 14 days had a moisture content of under 0.5%.

For the second batch, 16.93 kg of SA with a yield of 93.19% was obtained. The resulting SA was analysed for purity using GC-MS, which revealed a purity of 99%. Moisture content was analysed at 95°C, showing that samples that were dried at 50°C for 7 days had a moisture content of under 0.5%.

For the third batch, 16.96 kg of SA with a yield of 93.34% was obtained. The resulting SA was analysed for purity using GC-MS, which revealed a purity of 99%. Moisture content was analysed at 95°C, showing that samples that were dried at 45°C for 7 days had a moisture content of under 0.5%. The pilot production results are given in Table 3.

Table 2. Pilot-Scale Synthesis Trial Pattern of SA.

Parameter 1	Amount of wintergreen oil	1kg, 5 kg, 20 kg
Parameter 2	SA drying temperature	40°C, 45°C, 50°C
Parameter 3	SA drying time	7 days, 10 days, 14 days

Table 3. Pilot Production Results of SA.

1 kg batch	Total production time 15 days	Yield 92.47%, purity 98.25%
5 kg batch	Total production time 15 days	Yield 91.96%, purity 97.95%
First 20 kg batch	Total production time 15 days	Yield 93.92%, purity 99.16%
Second 20 kg batch (press filtered)	Total production time 8 days	Yield 93.19%, purity 99%
Third 20 kg batch (press filtered)	Total production time 8 days	Yield 93.34%, purity 99%

Pilot production runs with 1 kg, 5 kg and three batches of 20 kg of wintergreen oil produced SA with a yield range of 91.06-93.92% using green chemistry methods. The resulting SA batches had a purity of approximately 99%. This is a sufficient degree of purity for the SA to be used as a raw material in cosmetics products. Filtering the SA solution via a filter press had a reduced crystal drying time and brought down total production time to eight days.

DISCUSSION

SA is one of the most common active ingredients used in cosmetic products. It is an organic compound. It is a colourless crystal found naturally in various plants, such as willow bark or wintergreen. SA used in skin care products can be either natural or synthetic.

According to a report by the Regional Network Coordinating Organizations (RNCOs), which is an Indian based market research company, the world cosmetics market was valued at $233 billion in 2012, and is projected to reach $ 480,4 billion by 2030, with a compound annual growth rate of 4.6% (28, 29). In response to such anticipated growth, cosmetic brands are expected to keep abreast of customer needs and develop innovative products if they want to maintain their position in the market (28).

In 2012, global SA consumption was at 79,725 tonnes, and this figure is expected to climb to 149,652 tonnes in 2023. This indicates a compound annual growth rate of 6.5%. Total global sale revenue of SA was $239.5 million in 2012, and this is expected to rise to $546.8 million in 2023. This indicates a compound annual growth rate of 8.6%. The regional breakdown of the SA market for the year 2013 was as follows: North America 27.9%, Europe 34.9%, Asia-Pacific 25.3%, and other regions 11.9%. Natural cosmetic products account for around 1% of global cosmetics market (28, 30).

In addition to skin care products, SA is also included in hair care formulations to treat excessive oil and dandruff (31). It cleanses the scalp. It is used as an anti-dandruff agent in hair products (conditioners, shampoos) and in baby shampoos to prevent cradle cap. It is also used as a preservative to extend the shelf life of products (32). It inhibits the growth of various types of bacteria. SA is considered safe when used as a preservative in cosmetic products at a concentration of 0.5%, according to the Scientific Committee on Consumer Safety. SA has a strong antifungal effect. SA produced protein leakage into the medium, significant lipid degradation, and intracellular disarray in the pathogen. Having keratolytic effect and dissolving the superficial layers of the epidermis, SA has an important therapeutic effect on oily and problematic skin. It is also used in medicine for its analgesic and anti-inflammatory properties (33).

Using alternative solvents, reducing waste, increasing the efficiency of the different processes, improving economy in energy, and using safe chemicals are the main concepts of green chemistry. Solvents are required in these reactions to dissolve solids, enable transfer of material (extraction), stabilize transition states and to facilitate precipitation. Non-toxicity alone does not indicate that a certain product is compatible with green chemistry. Solvent reclamation, solubility, lack of toxic formations, atom efficiency, separation of product and solvent and ineffectiveness of solvent on end product are required factors to be compatible with green chemistry. Water as a molecular solvent offers high solubility with polar compounds besides being clean, cheap and having low reactivity. On the other hand, organic solvents are toxic, costly and flammable. 15 million kg of organic solvent is used globally every year. The primary mission of green chemistry is to find alternatives to these solvents.

Different from our study, Molleti and Yadav (34) prepared a new sulphated Fe_2O_3–ZrO_2 catalyst with altered iron loadings using the combustion technique and utilized in methyl salicylate preparation from SA and dimethyl carbonate. The methyl salicylate produced was reported to be widely useable in food and pharma industries. They also evaluated the effect of different kinetic parameters on the esterification rate of SA. They reported that optimum conditions for the 99% conversion of SA with the 100% selectivity to be 120°C after 150 min at a molar ratio of 1:10, SA to dimethyl carbonate.

In our study, filtering the SA solution via a filter press led to a reduced crystal drying time, and brought down total production time to eight days. As the SA production size increases (from 1 kg to 20 kg), one of the biggest problems is getting more moist solids after filtration. The filter press device is a special filtering device. During filtration, air is applied to the crystals, resulting in drier solids. In this way, the drying time of the solid is significantly reduced. Accordingly one of the most important parameters of green chemistry is to shorten the process time.

To obtain a marketable product, it is essential to create the necessary conditions for pilot production. Data obtained from laboratory-scale synthesis is used to increase production gradually to factory-scale. For this purpose, in our study, different batches of (1 kg, 5 kg, 20 kg) oil of wintergreen was prepared for the production of SA. Our results revealed a sufficient degree of purity for the SA to be used as a raw material in cosmetics products. Accordingly evaluation of production purity with GC-MS stands out as an important feature to support the results of our study.

Ethics Committee Approval: Ethics committee approval is not required because of no material or experimental animal that would require permission.

Peer-review: Externally peer-reviewed.

Author Contributions: Conception/Design of Study - G.Ö., T.S.; Data Acquisition - G.Ö., T.S.; Data Analysis/Interpretation - G.Ö., T.S.; Drafting Manuscript - G.Ö., T.S.; Critical Revision of Manuscript - E.E.A.; Final Approval and Accountability - G.Ö., T.S., E.E.A.

Conflict of Interest: The authors have no conflict of interest to declare.

Financial Disclosure: The authors declare that this study has received no financial support.

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