Various Topical Formulations of Salicylic Acid in Market: An Overview

Greeshma Surendran*, Khushi Kakde, Sanjana Mhatre, Aditya Sharma, Chinmay Patil,

Dr. Shrutika D Patil

*Corresponding Author

Lokmanya Tilak Institute of Pharmacy, Kharghar, Navi-Mumbai-410210.

1. Abstract

Salicylic acid (SA) comes from birch leaves and white willow bark, has become an important ingredient in both industrial and medical uses. The article examines the many functions of salicylic acid, with a focus on dermatological therapies for diseases including molluscum contagiosum, psoriasis, and acne vulgaris. SA is an effective keratolytic and antibacterial agent that can exfoliate skin, lower inflammation, and improve the absorption of other topical therapies. The relative efficacy of tretinoin and SA was evaluated in a randomized control trial, which showed comparable results with tretinoin responding more quickly. With a focus on its safety profile and possible adverse effects, the study also explores the chemistry of salicylic acid, its derivatives, and several topical forms. To further comprehend salicylic acid's pharmacokinetics, its absorption, distribution, metabolism, and elimination (ADME) are examined. Different formulations—such as gels, lotions, and shampoos—are examined in relation to their uses and therapeutic advantages. In its conclusion, this study highlights the significance of salicylic acid in modern dermatological treatment while outlining potential directions for further investigation to improve formulation effectiveness and patient safety.

Keywords: Salicylic acid, Acne vulgaris, Formulations, Antibacterial agent, Keratolytic, Tretinoin

2. Introduction

A naturally occurring compound called salicylic acid (SA) has long been utilized in both medicine and the chemical industry. It is naturally made up of birch leaves, white willow bark, and certain savoy tree species[1]. Since Salix alba, or white willow, is a naturally occurring source of this acid, salicylic acid (SA, 2-hydroxybenzoic acid) gets its name from the Latin Salix, which means a willow tree. Salicylic acid is an important organic acid used in industry.It has a crystalline powder form. Salicylic acid has fewer adverse effects and is a gentler, safer therapy for mild to severe acne vulgaris. It functions as an exfoliator and mostly treats comedonal acne by reducing follicular cell shedding and obstructing congestion.The effectiveness of salicylic acid and tretinoin (both in conjunction with clindamycin) was evaluated in a 12-week randomized control experiment. The results showed that both were equally effective, with tretinoin working faster. Creams, gels, solutions, cleaners, soaps, and foams with a dose of 0.5% to 2% are advised. Use between one and three times daily.

Chemical formula- C7H6O3 [2]

Melting point- Between 157 and l59 C.

pH-2.4(acid) pKa is 2.98 and logK is equal to 2.26

Solubility- Very soluble in organic polar solvents as well as water [3]

As a plant hormone, SA plays a vital role in photosynthesis, transpiration, ion absorption, transportation, and plant growth and development[4]. Among the class of phenolic compounds that are naturally generated by plants. Many microorganisms create SA, mostly through the production of chorismic acid, a crucial step in the shikimic acid pathway, the sole bacterial route that leads to the biosynthesis of aromatic chemicals. The Kolbe-Schmitt technique, named after Hermann Kolbe and Rudolf Schmitt, is the most extensively used method for commercially producing SA.A total of thirty-six plants from various groups have had their salicylic acid described .It has been demonstrated to trigger defense systems in plants in reaction to biotic and abiotic stimulation, particularly reactive oxygen species. Key antioxidant enzymes such as glutathione reductase (GR), ascorbate peroxidase (APX), and superoxide dismutase (SOD) are activated together with non-enzymatic antioxidants such glutathione and acetylsalicylic acid[5]. Salicylic acid derivatives are mostly utilized in medicine to treat cardiovascular and rheumatic Conditions. Treatment for skin conditions and lesions is also provided by it in medicine. Salicylic acid exfoliation treatments, or chemical peels, are used in surgical cosmetic treatments. It is especially advised for oily, seborrheic, acne-prone complexions, hyperpigmentation, and to slow down the processes linked to skin aging because of its keratolytic and antibacterial properties. This acid can function as a preservative as well as an active component in cosmetic goods. It is the primary member of the betahydroxy acids (BHA) group. It belongs to both the alcohol and acid groups, so it may undergo responses specific to each group. a few example of this is the treatment of psoriasis, where salicylic acid preparations are used to remove scales. Keratolytic items that included salicylic acid are also used to treat dandruff, seborrheic dermatitis, calluses, corns, knuckle nodules, and warts. Because of its fungicidal and bactericidal qualities, it is utilized in cosmetics as a preservative in addition to being an active element. It maintains the cosmetic in an undisturbed microbiological state both during and after manufacture. It brings the product's pH down to a level where microbes cannot survive.

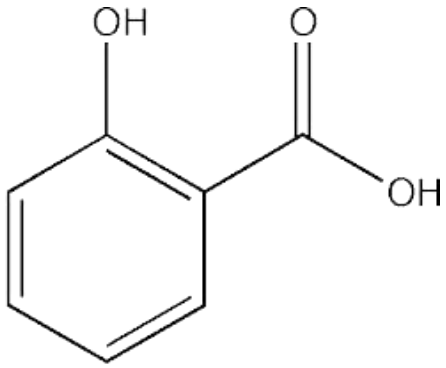
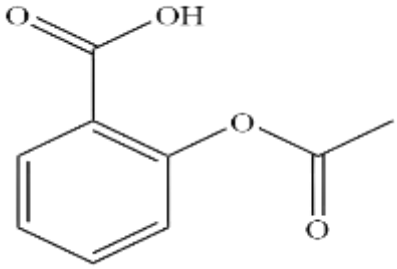
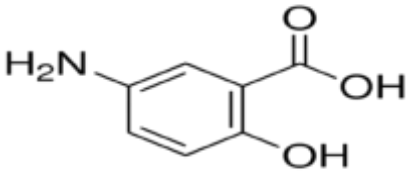
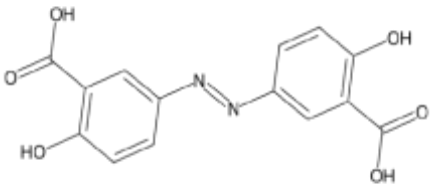
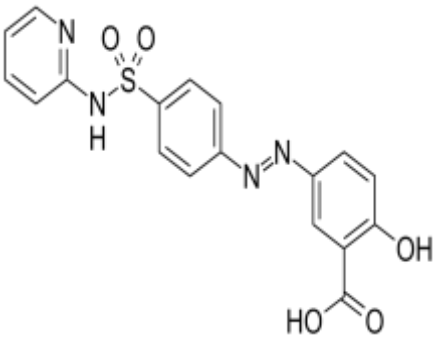


Figure 1: Structure of Salicylic Acid [5]

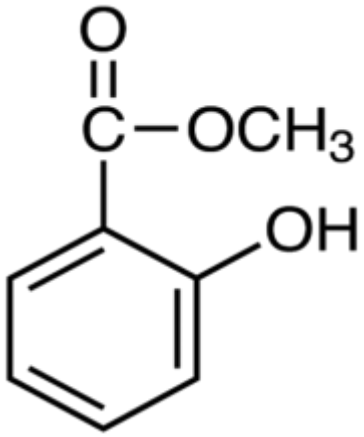
Salicylic acid is a tiny, lipophilic molecule, it may dissolve in fat and enter the epidermis quickly and easily. This acid dissolves the intercellular cement by interfering with the stratum corneum. It affects the ionic connections that pass from the stratum corneum to the stratum spinosum between the dead epidermal cells known as corneocytes. It affects the Cuti Bacterium acnes bacteria as well. It works by penetrating the sebaceous glands and opening up the follicular orifices, which helps to lessen the development of non-inflammatory skin lesions and ease those that already present.It also controls epidermal exfoliation and lowers dilated pores on the skin, as well as the production of sebum by sebaceous glands.[6,7,8,9,10]

Salicylates are the salts and esters of salicylic acid. From a chemical standpoint, salicylic acid is a member of a broad class of plant phenolics that have an aromatic ring with a hydroxyl group or compounds with similar functional properties. In an aqueous solution, aspirin, an analog of salicylic acid, spontaneously hydrolyzes to produce salicylic acid. As a chemical substance, it has a carboxyl group (-COOH) in its molecule and a hydroxyl group (-OH) attached to the beta carbon atom (Figure 1)[5,11].

Table 1: Salicylic acid derivatives

Name of the derivative	Structure	Reference
Acetylsalicylic acid- Acetylsalicylic acid is the most often used medication. Aspirin has a variety of physiological effects, the most notable of which are the lowering of fever, analgesia (pain relief), thrombosis prevention, and inflammation.		**[12]**
Mesalazine-5- aminosalicylic acid (5-ASA)) (6), also known as mesalazine, is an anti-inflammatory medication used to treat ulcerative colitis (UC), which is inflammation of the digestive tract.		**[13]**
Olsalazine- An anti-inflammatory medication called olsalazine is used to treat inflammatory bowel conditions like UC.		**[14]**
Sulfasalazine- A sulfa medication, sulfasalazine is derived from mesalazine and is mostly used as an anti-inflammatory agent to treat inflammatory bowel disease, rheumatoid arthritis, and arthritis associated with enthesitis, such as juvenile spondyloarthropathies.		**[15]**

Methyl salicylate-
It is used as a flavoring in medicines, candy, food, and drinks. Similar to meadowsweet, root beer, and magnolia, it is used as a perfumery. In cosmetics, it serves as an ultraviolet absorber, odorant, and perfume. In medicine, this chemical is mostly utilized for analgesia and dephlogistication.



[16]

In oral treatment, salicylate is quickly absorbed through passive diffusion of unionized stomach-derived lipophilic compounds High levels of salicylate. Additionally, ate absorption is place in the jejunum and tiny intestinal due to its surface area. A passive process seems to be the cause of small bowel salicylate absorption of salicylate.Despite the fact that aspirin can hypnotically Due to its slowness, there is little to no free In the gut, salicylate is absorbed as Instead of salicylic acid, apirin Salicylate can also be absorbed through the rectal route, and It is possible for cutaneous absorption from salicylate with rubefacients in it .

Salicylates are widely dispersed throughout bodily fluids after absorption. Adults' reported apparent volume of distribution (Vd) of salicylate ranges from 9.6 to 12.7 L, whereas children's Vds range from 0.12 to 0.14 L/kg.

It has been demonstrated that synovial fluid has much less protein binding of salicylic acid than plasma. While the overall concentration of salicylic acid in synovial fluid is lesser than that in plasma, which is probably because to the fluid's lower levels of albumin. The quantities of aspirin in synovial fluid are similarly substantially lower than those in plasma, but they peak considerably later, and aspirin stays in the synovial fluid for a considerable amount of time after it has vanished from the plasma.

It has been discovered that the salicylic acid content in saliva is proportionate to the plasma concentration. Nevertheless, the concentration may change depending on the pH of the saliva at the manufacturing site, and it has been proposed that this approach is inappropriate for regular salicylate concentration monitoring.

Fetal plasma concentrations at delivery are greater than contemporaneous maternal amounts of salicylic acid, which easily crosses the placenta .Salicylate is easily absorbed through breast milk, and while a nursing newborn may only get a little quantity after a single dosage, if the mother consumes high quantities on a regular basis, the baby may be exposed to significant amounts of salicylate.

Between 28 and 35 percent of the aspirin hydrolysis during absorption is caused by aspirin esterase activity in the gastrointestinal mucosal membranes. Although there may be significant age, sex, and illness-related variations in tissue activity, this esterase activity is highest in the mucosal cells of the gastric fundus. For instance, people with alcoholic liver disease had lower aspirin esterase activity. During the first 20 minutes after consumption, aspirin predominates in the plasma and is detectable for a number of minutes before any detectable salicylic acid is present. The aspirin concentration is significantly reliant on the velocity of absorption since it then quickly leaves the circulation.Aspirin pharmacokinetics have also been shown to vary throughout the day.

Salicylic acid undergoes partial metabolism and partial excretion unaltered. In addition to being actively released by the proximal tubule, free salicylic acid diffuses easily throughout the glomerulus. Due to their reliance on tubular secretion and glomerular filtration, salicylic acid conjugates are likewise eliminated by the kidneys. Gentisic acid, a hydroxylated metabolite, is eliminated similarly to free salicylic acid[17].

3. Various topical formulation of Salicylic Acid in market:

3.1. Salicylic acid in acne vulgaris:

Although it is less effective than topical retinoids, salicylic acid, a lipid-soluble phytohormone with comedolytic qualities, is nevertheless a somewhat good therapy for acne[18]. The SA cleanser and the BPO wash, a topical bactericidal agent frequently used as a first-line therapy, were compared in a crossover research. In order to cure acne vulgaris, thirty individuals received after two weeks of using a 2% SA cleanser revealed a notable improvement in their acne (measured by fewer comedones), which then got worse while using the washing BPO[19]. SA is also beneficial when used in conjunction with other therapies. 60 individuals with active acne participated in a comparison trial between oral isotretinoin and oral isotretinoin with a 20% SA peel; the combo therapy proved more successful than isotretinoin alone (a 93% fewer lesions than before, as opposed to 73%[20].

- Acne vulgaris is largely caused by dysbiosis of the facial microbiota. The objective of the current investigation was to examine the impact of 2% Supramolecular Salicylic Acid (SSA) on face microorganisms linked to acne. Thirty individuals with acne vulgaris was treated with 2% SSA for eight weeks and ten chose people who did not have face acne were selected. In this study,the reaction of thirty individuals with mild acne vulgaris to a 2% SSA therapy was examined,along with the microorganisms on their faces. It has been shown that dysbiosis in the microbiota of the face can cause acne to appear. The 2% SSA intervention led to a notable improvement .Just two patients, who healed on their own, had very minimal side effects and a moderate acne patient's global acne grading system (GAGS) score. According to the results of the metagenomic investigation of the pre-treated and treated group, 2% SSA influences the microbial diversity of patients in a way that is similar to that of those without facial acne[21].
- Combined chemical peel and topical salicylic acid based gel combination in the treatment of active acne- A person's quality of life can be significantly impacted by acne vulgaris. In order to avoid mental harm and long-term issues, action must be taken against it.The purpose of this study was to show that mild to moderate acne might be improved with a chemical peel when combined with a purifying and exfoliating solution for at-home maintenance. Methods: The research comprised 45 participants with mild to moderate acne. Patients received a chemical peel consisting of a combination of retinoic acid, pyruvic acid, and salicylic acid once every three weeks for four sessions. Following the healing phase, patients also received home care. Patients' happiness and skin improvement were assessed using the Face Skin Q questionnaire, Subject Global Aesthetic Improvement Scale and Michaelson's acne severity score .Result:All patients experienced improvement in skin lesions following four chemical peel treatments, as measured by Michaelson's acne severity score and Subject Global Aesthetic Improvement Score. Every patient who had treatment had a higher quality of life, according to the Face Skin Q questionnaire.In conclusion, a combination of exfoliating home care treatments and chemical peels based on salicylic acid seems to be a highly effective approach to treating acne. As a result, the doctor may prescribe this mixture to individuals who are suffering from acne vulgaris[22].

3.2. Salicylic acid in treatment for molluscum contagiosum in children:

To ascertain if the use of phenol solution or salicylic acid gel has an impact on children's molluscum contagiosum (MC) lesion clearance. Patients and techniques: For the treatment of MC in children, this trial was prospectively controlled, randomized, and had two treatment arms and one vehicle arm for the treatment of MC in children trial was conducted in the outpatient dermatological clinics of a district general hospital and a teaching hospital. Over the course of four years, 114 children between the ages of one and fifteen were recruited in the study; 83 of them finished it. Randomization was used to assign patients to one of three treatment groups: once or twice a week, 12% salicylic acid gel, or a monthly application of 70% alcohol and 10% phenol in 70% alcohol. Every patient was also given a daily aqueous cream to help with their eczema. Every month, they came back to the clinic for MC lesion counting and therapy. They were examined for a full resolution or for a maximum of six months, whichever came first. The findings imply that topical salicylic acid may help speed up the resolution of MC in youngsters. The application of diluted phenol appears to have little effect on the disease's course[23].

3.3. Salicylic acid in psoriasis-Microemulsions (MEs):

These are transparent and thermodynamically stable systems. They were employed to dissolve medicines and increase topical medication availability. Salicylic acid (SA) is a keratolytic agent that has antibacterial properties. This study sought to create an optimal SA micro emulsion gel for slow, variable, and imperfect oral medication absorption in psoriasis patients. The dispersion solubility of SA was investigated in various oils, surfactants, and co-surfactants, and the micro emulsion area was determined by generating a pseudo phase ternary diagram. The optimized microemulsion formulations were tested for thermodynamic stability. After the stability study, the micro emulsion gel was prepared and characterized for spreadability, viscosity measurement, drug content, in vitro diffusion, and in vitro release data. The stable formulation was then characterized for droplet size, pH determination, centrifugation, percent drug content in micro emulsion, zeta potential, and vesicle size measurement. Based on the solubility experiment, labrasol was selected as a surfactant, plurol oleique as a co-surfactant, and neem oil as an oil component. The improved formulation contained SA 0.05 (%w/w), labrasol (24%), plurol oleique (8%), and neem oil (8%). The in vitro drug release from SA micro emulsion gel was demonstrated to be substantially greater than that of the pure drug.The in-vitro diffusion of micro emulsion gel worked very effectively.This study suggests that incorporating SA into micro emulsion gel can improve its solubility and permeability[24].

3.4. Salicylic Acid in microbial infections:

Since times past, salicylic acids have been utilized in both human and veterinary medicine for their analgesic, anti-inflammatory, and antipyretic effects. Research on their botanical origins initially revealed a crucial function of salicylic acid: immunological regulation in response to microbial infection. Salicylic acid has a variety of impacts on the physiology of bacteria. They frequently apply selection pressures that result in the emergence of antimicrobial compound cross-resistance. The multiple antibiotic resistance (mar) operon in Escherichia coli is activated by salicylic acid, which lowers antibiotic sensitivity. This relationship was first described in this strain of bacteria. Research indicates that closely related Enterobacteriaceae have comparable presentations when the mar phenotype is stimulated. By hindering the formation of biofilms and boosting persister cell populations, salicylic acids also impact the pathogenicity of several opportunistic infections. To shed light on possible connections between ambient microorganisms and their therapeutically relevant antimicrobial-resistant cousins, it is essential to comprehend how salicylic acid affects bacteria from different backgrounds. In addition to offering insights into potential ways to strengthen existing treatment options, this review updates knowledge on the effects

of salicylic acid and its major derivatives on a range of bacterial pathogens and highlights the cellular regulatory networks that have been established during the investigation of this significant class of drugs[25].

Table 2: Various topical skin formulation of salicylic acid in market

Sr No.	Brand Name	Active Ingredients	Uses	Company Name
1	Salicylix Sf6	Salicylic Acid IP 6%w/w	Used for the treatment of acne	Eris Lifesciences Ltd
2	Salicylic Acid and Hyaluronic Acid Gel	Zinc Oxide Titanium Dioxide Tocopheryl Acetate	Managing breakouts and combating aggressive acne.	CiplaHealth

- Contraindications-Those who are hypersensitive to salicylic acid, have acute or chronic renal insufficiency, have acute or chronic hepatic dysfunction, or have gastritis or peptic ulcer disease should not take it. Additionally, using trilisate preparations and other salicylate-containing products at the same time can raise plasma levels of salicylate, increasing the risk of toxicity.

- Adverse effect-Erosive gastritis, gastrointestinal bleeding, and nausea are side effects of magnesium salicylate treatment . According to reports, choline magnesium trisalicylate causes less blood loss in the feces than aspirin. Nonacetylated salicylates have less of an impact on platelet function than aspirin, yet high dosages may result in hypoprothrombinemia. Salicylic Acids effects on the central nervous system include headache, lightheadedness, sleepiness, disorientation, blurred vision, delirium, seizures, coma, tinnitus, hallucinations, and thirst. Severe metabolic acidosis is also linked to salicylate poisoning, with or without respiratory alkalosis that compensates . Hyperpnea is one of the adverse respiratory consequences that might happen with alkalosis of the respiratory system . Salicylate treatment may also result in rash with urticaria and pruritus.

Table 3: Various Hair formulation of salicylic acid in market

Sr No.	Brand Name	Active Ingredients	Uses	Company name
1	Salisia Kt Shampoo	Salicylic Acid IP 2.0% w/v Ketoconazole IP 2.0% w/v	Antidandruff shampoo	Ajanta Pharma Ltd
2	Haironic Salicylic Acid Exfoliating Scalp Oil & Flake Control Hair Serum	Salicylic acid infused with Rice Tien Extract, Flaxseed Liquid Extract, Green Tea Extract, Grape seed Extract & Aloevera Extract	Growth Stimulating, Volumizer, Anti-greying.	Haironic Hair science

- Adverse effect
  Irritating responses can happen sometimes. After washing, dogs and cats may exhibit itching and/or irritated skin.
- Contrainteractions
  Sulfur and salicylic acid work in concert.

Acute or chronic salicylism, or the syndrome of salicylic acid poisoning, occurs when blood salicylate concentrations exceed 35 mg/dL. Salicylism can cause delirium, nausea, vomiting, stupor, coma, psychosis, disorientation, dizziness, and even death. At these levels, the medullary respiratory center is triggered, resulting in respiratory alkalosis and hyperventilation. Acidosis, hypoglycemia in youngsters, and hyperglycemia in adults are examples of metabolic disorders that can also happen. Due to effects on cochlear hair cells and increases in labyrinthine pressure, salicylate poisoning results in tinnitus. Topical use of 6% salicylic acid across as little as 40% of the body's surface area can result in salicylism, or salicylic acid poisoning. Thirteen cases of psoriasis, eight cases of ichthyosis, two cases of tinea imbricata, one case of erythroderma, and one case of seborrheic dermatitis had toxicity that was directly associated to topically applied salicylic acid, according to a PubMed search conducted from 1966 to the present. Frequently, toxicity developed a few days after usage. The most severe occurrences, which resulted in comas and deaths, were psoriasis sufferers. When used for back pain, topical methyl salicylate at a concentration of 10% and 3% menthol showed no adverse effects; toxicity occurred at greater doses and longer application times. Topically administered wintergreen oil containing 98% methyl salicylate has been linked to toxicity. Reversible constriction of the fetal ductus arteriosus following maternal usage, salicylism in a psoriasis patient, local necrosis and interstitial nephritis, and an increase in the anticoagulant effect of warfarin are among the documented toxicities. When administering topical salicylic acid, more caution should be taken for children and disorders involving vast body surface regions, such as ichthyosis and psoriasis[26].

4.Conclusion

The investigation of topical synthetic formulations for improving cosmetic applications and curing microbiological illnesses, in summary, demonstrates noteworthy progress and encouraging possibilities. These formulations, which combine cutting-edge components and delivery methods, successfully target certain diseases while also enhancing the look and health of the skin. These products serve both therapeutic and cosmetic purposes, which makes them indispensable in contemporary dermatological and cosmetic practice. Future studies should concentrate on refining these formulations for increased efficacy, safety, and user experience in order to fulfill changing consumer desires while upholding strict scientific guidelines. Future topical therapies with more efficacy and versatility will be made possible by the incorporation of these discoveries as skin microbiology and formulation science become increasingly complicated.

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