THE SCIENCE SUPPORTING UNAGEL®
A pH Neutralized Salicylic Acid Acne Treatment

Abstract
Salicylic Acid (SA) or 2-Hydroxybenzoic acid is commonly referred to as a beta hydroxyl acid (BHA). Since ancient times, humans have benefited from the therapeutic effects of naturally occurring SA precursors, which readily metabolize to SA and provide analgesic, anti-inflammatory and antipyretic benefits. Although SA can occur naturally as an organic acid, SA itself is rarely found in nature. It is synthesized commercially via the Kolbe-Schmitt reaction. Today, salicylic Acid continues to play an important role as an active ingredient in over-the-counter (OTC) topical drug products. SA is a relatively small molecule (C7H6O3) which is more acidic (pKa 3.0) than most organic acids. The USP-grade SA employed as an active ingredient for OTC drug applications must be minimally 99.5% pure SA. SA is a keratolytic agent that induces corneocyte disaggregation in the upper stratum corneum, thereby enhancing the shedding of scales and softening the stratum corneum.[2] Salicylic Acid products currently in the market have a pH between 3 & 4. A limitation of the currently available keratolytic topical formulations is their potential to cause such unwanted reactions as stinging, burning, and erythema due, in part, to their rapid absorption and erratic peak-trough concentrations.[1,2,3]

Unagel®, by Advanced Skin Technology is a novel formulation in that it utilizes a technology that addresses the treatment of acne with little or no irritation of the skin. This is achieved because salicylic acid in Unagel® is in its partially neutralized form with little free, non-dissociated SA and much reduced dermatotoxicity unlike current products on the market. The unique natural extracts in Unagel® with anti-inflammatory activity boosts the therapeutic activity of the product, since acne is an inflammatory skin disorder responsive to a number of factors. Unagel® also works synergistically with a retinol product imparting a high potency acne treatment. Recent studies have demonstrated the clinical efficacy of topical retinoids in maintenance therapy of acne. These claims support the currently refined understanding of acne as a chronic disease.[4]

Acne and Salicylic Acid
Acne vulgaris is a disorder of sebaceous follicles that has multiple factors contributing to its onset. It is associated with an increase in sebaceous gland activity, insufficient shedding of cellular debris plugging the gland’s duct and follicle, and proliferation in this oil-rich medium of the bacterium Propionibacterium acnes (P. Acnes). The excessive accumulation of sebum and bacteria in the pilosebaceous unit leads to formation of pustules, inflammatory papules and cysts.
Treatment of acne is generally focused on addressing the four major pathogenic factors of acne, namely increased sebum production, *Propionibacterium acnes*, abnormal follicular desquamation, and inflammation. The overall goal of acne management is to select treatment that addresses as many of these factors as possible while minimizing side effects (Katsambas, Stefanaki, & Cunliffe, 2004). Using multiple agents at the same time during treatment (concomitant therapy) has been recommended as a rational means to achieve this goal. Early acne lesions are non-inflammatory (open and closed comedones) which may develop into inflammatory (papules, pustules, and nodules). Most cases of acne exhibit a mixture of non-inflammatory and inflammatory lesions; however, some patients may present with predominantly non-inflammatory or inflammatory lesions. Pitted scars may result after acne lesions have resolved. The pathogenesis of acne is complex and multifactorial, and parallel targeting of various pathogenetic factors with appropriate OTC drugs such as salicylic acid and benzoyl peroxide currently represents the most prevalent and effective approach for treating this psychologically and physically scarring disease. Salicylic acid affects the arachidonic acid cascade and has anti-inflammatory properties. Moderate comedonal acne is treated similarly to mild comedonal acne. Topical retinoids, salicylic acid, azelaic acid, and benzoyl peroxide are commonly used. The combination of salicylic acid and benzoyl peroxide is irritating and not approved for use by FDA. Benzoyl peroxide has mild comedolytic but, as yet, no proven anticomedogenic effects on microcomedones. The drawback of the substance is its irritative potential.

According to Federal Register: March 4, 2010 (Volume 75, Number 42) Rules and Regulations 21CFR Part 333]- The approved active ingredients for an acne product are salicylic acid 0.5 to 2%, Benzoyl peroxide 2.5 -10%, Sulfur 3.0-10% and Resorcinol (not widely used) when combined with Sulfur in the approved combination.

The Cosmetic Ingredient Review Expert Panel concluded that salicylic acids are safe to use when formulated to avoid skin irritation and to be non-photosensitizing, or when directions for use include the daily application of sun protection. [5] Sufficient data is not available to establish a limit on SA concentration or to identify the minimum pH of formulations to inhibit skin irritation. SA absorbs light in the UVB range with peak absorbance at ca.300 nm and is a weakly fluorescent molecule. This later attribute is used for quantitative detection of SA deposition and retention on the skin via fluorescence spectroscopy. Salicylic acid is sparingly soluble in water, readily soluble in polar organic solvents and is able to penetrate the sebum rich milieu of the pore. Within the pore it is able to loosen the comedonal plug and exert some low level anti-inflammatory effects [6].

**Mechanism of Action**

Salicylic acid works by softening keratin, a protein that forms part of the skin structure. This helps to loosen dry scaly skin making it easier to remove. When salicylic acid is included in combination with a retinoid it exfoliates the stratum corneum allowing the retinoid to better penetrate the skin.

In acne, salicylic acid helps facilitate the shedding of the cells inside the follicles, preventing sebaceous gland from clogging. Salicylic acid also works to break down blackheads and whiteheads.
Neutralized Salicylic Acid

SA at close to neutral pH (mostly in its neutralized form as salicylate, pH 6.50) exerted a corneodesmolytic activity as good as that of salicylic acid in an acidic vehicle (pH 3.12) after only two days of application. Furthermore, the performance of glycolic acid and salicylic acid salts as exfoliants were compared at pH 6.50.

When these two hydroxyl acids were formulated at the same molar level in a cosmetic base (14.47mmol L⁻¹), the salicylic acid preparation gave an 8.2% increase in stratum corneum desquamation compared with the glycolic acid preparation ($P < 0.05$). The corneodesmolytic effects were confirmed using a tape-stripping assay combined with a quantitative protein assay. Neutralized salicylic acid was found to enhance the removal of stratum corneum proteins significantly more than the vehicle after 25 sequential tape stripings (14%; $P < 0.05$).

In another published study,[7] the keratolytic efficacy of salicylic acid aqueous solution at pH 3.3, 2% salicylic acid aqueous solution at pH 3.3 with menthol and 2% salicylic acid aqueous solution at pH of 6.95 was compared with aqueous vehicle control at a pH of 7.4. The results indicated that a statistically significant mass of stratum corneum was removed after 6 hr and 20 tape strips in all three test groups (SA pH 3.3, SA pH 3.3 with menthol, SA pH 6.95) compared with vehicle, untreated and untreated but occluded groups.

In a published report, a stinging test was performed according to the Frosch & Kligman method, to assess the suitability of neutralized salicylic acid as an ingredient for sensitive skin by evaluating the influence of the formulation base-pH on stinging potential. Salicylic acid formulated at pH 6.50 induced no stinging sensation (score 0) in contrast to salicylic acid at pH 3.12 (score 19; $P < 0.05$). In addition, a clinical study was conducted to assess the erythema induced on volunteers’ cheeks after a single application of a neutralized salicylic acid (1%) formulation compared with placebo. Visual redness was assessed by a dermatologist and then measured with a Mexameter. No significant differences were observed. Moreover, half of the panel had sensitive skin and no correlation could be established between redness and/or abnormal sensation and sensitive skin. In conclusion, neutralized salicylic acid at a 1% concentration is a suitable exfoliant agent for subjects with sensitive skin.[8]

Poria Cocos and Phragmitest Kharka Extract and Acne

These extracts, used extensively in Chinese and Far eastern medicine, work jointly with salicylic acid to control and reduce inflammation of acne lesions. It is well known that the topical use of salicylic acid can increase sun sensitivity causing an interesting dilemma. It appears that salicylic acid may be able to reverse some of the damage caused by photoaging, but at the same time it makes the skin more susceptible to photoaging. The combination of Kharka and Poria extracts have been known to show reduction of itching on the skin after histamine induced and UV-induced skin irritation with reduction of erythema. Triterpene carboxylic acids and derivatives in poria extract are responsible for its anti-inflammatory effects. [9]
Conclusion

Unagel® utilizes neutralized salicylic acid with anti-inflammatory extracts affords safe, non-irritating and effective treatment of acne. Salicylic acid must be used continuously to prevent the clogging of pores and the return of acne. Skin pH is typically used as a criterion to predict the possible irritation capability in a product. Most currently marketed OTC acne products containing salicylic acid have a pH of less than 4.0 which can cause stinging, burning, dryness and skin irritation. Unagel® achieves the goal of acne treatment by unplugging skin pores and removing dead skin cells which can trap acne causing bacteria. Unagel® offers sustained release of salicylic acid at a skin friendly pH to treat acne which exhibits a mixture of non-inflammatory and inflammatory lesions. The omnipotent blend of Phragmites kharka and Poria cocos in Unagel® has a barrier repairing and barrier maintenance function with anti-inflammatory effects.

References


