Chapter 2
Acid peels

In the mid-1990s, dermatologists turned their attention to hydroxy acids. The official recognition of these substances was preceded by a long history of their practical application. Sour milk, sugar cane juice, wine sediment, fruit, and berry juices have been used for skin rejuvenation since ancient Egypt and ancient Greece. As we already know today, some of the key active components of these products are lactic, tartaric, glycolic, and other fruit acids, which by their chemical structure, belong to the hydroxy acids.

Ruey Yu and Eugene van Scott

American dermatologists Ruey Yu and Eugene van Scott were the first to study the effects of these substances on the skin in detail. Studying hyperkeratosis conditions (e.g., ichthyosis), they showed that hydroxy acids weaken the bonds between the corneocytes, facilitating their desquamation. At the same time, unlike keratolytic agents, hydroxy acids do not denature proteins, so there is no frost on the treated area.

In addition to their exfoliating effects, hydroxy acids have been found to have other valuable properties. Today, hydroxy acids are some of the most studied and popular ingredients in topical products, which are used for skin care in various conditions and for treating specific pathologies.

2.1. Hydroxy acids: chemical structure and classification

Organic substances containing several functional groups are called compounds with mixed functions. Such compounds include hydroxy acids having an alcohol (hydroxyl) group –OH and an acid (carboxyl) group –COOH. It turns out that a hydroxy acid is both an acid and an alcohol compound.

According to a common nomenclature variant, the carbon atom to which the carboxy group is attached is designated by the letter α, the next following atom by β, and so on following the Greek alphabet. In the case of sufficiently long chains, the atom furthest from the carboxyl is usually designated ω. Accordingly, if the hydroxyl group (hydroxy group) is located at the α carbon atom, the compound is called α-hydroxy acid (AHA), β-hydroxy acid (BHA) at the β atom, and so on.

The hydroxy acid molecule can contain several carboxy groups. The number of these groups is used to distinguish mono-, di-, and tricarboxylic acids. Some hydroxy acids can be classified as both AHAs and BHAs because they have a hydroxyl group in the α-position with respect to one carboxy group and in the β-position with respect to another carboxy group (**Table II-2-1**). Examples are malic and citric acids, although their chemical properties (including solubility in water) are still closer to AHAs.

Table II-2-1. Classification of hydroxy acids (with examples)

α-HYDROXY ACIDS (AHAs)	β-HYDROXY ACIDS (BHAs)	POLYHYDROXY ACIDS (PHAs)
• Monocarboxylic: glycolic, lactic, almond • Dicarboxylic: malic, tartaric • Tricarboxylic: citric	• Propionic • β-Hydroxypropionic • Tropic	• Lactobionic • Gluconic

There can also be another version: one carboxyl group and several hydroxyl groups. Such compounds are called polyhydroxy acids (PHAs). PHAs are widely spread and synthesized by cells from hydrocarbon compounds (including sugars) during carbohydrate metabolism reactions.

AHAs have found wide applications in skincare. These water-soluble compounds are included in emulsion and water-gel preparations, the essential characteristic of which is the pH value.

BHAs are generally less water soluble than AHAs. In addition, the mechanisms of their action, the possible positive effects on the skin, and, most importantly, the safety issues are poorly studied, so the BHAs mentioned in the **Table II-2-1** are not used in cosmetics.

As for salicylic acid, it is often referred to as BHA. However, from a chemical point of view, this is incorrect because, in the salicylic acid molecule, both functional groups (carboxylic and hydroxyl) are attached directly to the benzene ring, not to the hydrocarbon chain. This fact determines salicylic acid's chemical properties and mechanism of action on the skin. Salicylic acid is insoluble in water, and its action on the skin is associated with the denaturation of proteins and does not depend on pH value. In this respect, salicylic acid is closer to phenol and is a keratolytic agent. This point is fundamental because it explains not only the different clinical effects of salicylic acid and AHAs, but also the different approaches to developing skincare formulations and recommendations for their use. For this reason, this chapter does not discuss salicylic acid, and information about it is given in Part II, section 1.4.

Two PHAs are used in dermatology and skincare practice: lactobionic acid and gluconic acid (and its derivative, gluconolactone). They are characterized by a pronounced moisturizing and extremely mild exfoliating effect, which makes them indispensable for the care of pathologically dry skin (ichthyosis, psoriasis).

2.2. Mechanism of action

The «leverage» of acid peeling on the skin is the change in its pH. The pH (potential of hydrogen) value is defined as the negative decimal logarithm of the concentration of hydrogen ions: pH 7 is called neutral, pH less than 7 is acidic, and more than 7 is alkaline.

The pH value of water reflects its acid-alkaline balance, which has a significant influence on the biochemical reactions taking place in the aquatic environment. In our body, the pH value in cells and intercellular fluids is slightly alkaline and is maintained at 7.0–7.3, while in blood, the pH is slightly higher, at 7.35–7.45. But in lysosomes (the cell organelle where enzymatic digestion of macromolecules takes place), the environment is acidic: here, the concentration of hydrogen ions is more than 100 times higher than in the cytoplasm, so pH is within 4.5–5.5.

No living cells exist in the *stratum corneum*, so the pH situation is quite different. Through the *stratum corneum*, the pH changes smoothly from an acidic 4.6–5.5 in the hydrolipid mantle to a slightly alkaline 7 at the border with the granular layer. This is an extreme pH difference, and it occurs within the thin *stratum corneum*. **Figure II-2-1** shows how the pH changes within the *stratum corneum*.

The pH gradient is a key factor in regulating enzymatic activity within the *stratum corneum*. This activity is different. Proteolytic enzymes (closer to the surface) cleave corneodesmosomes and provide exfoliation of corneocytes. In the lower layers of the *stratum corneum*, other enzymes are active: some are responsible for transforming keratinocytes into corneocytes, and others for forming intercellular lipid structures that form a lipid barrier.

All enzymes have their pH optimum: some are more active in an acidic environment, others in a more alkaline one. A pH deviation from the optimum inevitably affects the enzymatic activity: it decreases to a complete stop.

If a preparation whose pH differs significantly from 5.5 is applied to the skin surface, the surface pH value and the pH gradient through the *stratum corneum* change. This means that the enzymes of the *stratum corneum* find themselves in unphysiological conditions, and there is a failure in their work — everything they «worked on» at that moment turns out wrong. During the natural renewal of the epidermis, the defective horny scales reach the surface and peel off in a few days. Ordinarily, we do not see scaling because the normal horny scales are too small. In contrast, after acid peeling, the flaking is visible — larger abnormal horny scales formed at the time of the shock change in pH leave the skin.

In addition to enzyme failure, the pH change affects the structures maintaining the integrity of the *stratum corneum*, namely:

- intercellular lipid layers that «glue» corneocytes;
- corneodesmosomes which are protein bridges between neighboring corneocytes, ensuring their adhesion to each other.

These structures contain molecules with charged groups with electrostatic interactions. These interactions weaken as the pH environment changes, making the *stratum corneum* looser and less strong.

Thus, the change in pH gradient through the stratum corneum «hits» three key points controlling the formation and integrity of the skin barrier (**Fig. II-2-2**):

1) *stratum corneum*'s enzymes;
2) intercellular lipid layers;
3) corneodesmosomes.

It should be noted that the pH gradient through the *stratum corneum* changes when both acid and alkali are applied to the skin surface. In both

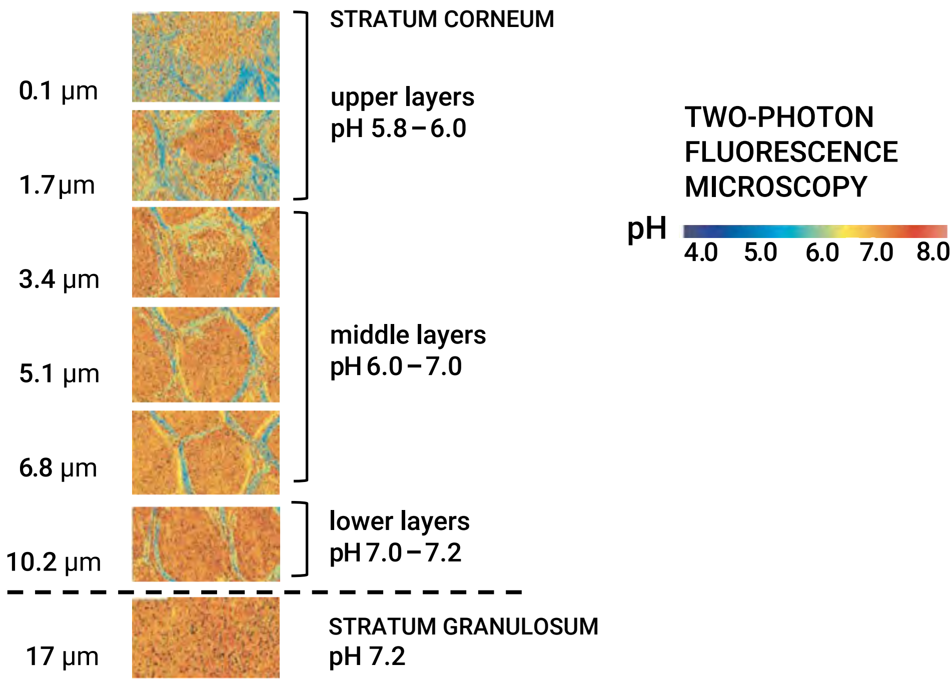

Figure II-2-1. pH gradient through the stratum corneum: measurements by two-photon fluorescence microscopy (Hanson K.M. et al., 2002)

Special molecules — fluorescent probes — are applied to the skin. They penetrate the *stratum corneum* and, under subsequent irradiation with light of a specific wavelength, go into an excited state and then give off excess energy in the form of photons of light. This secondary radiation is called fluorescence and can be recorded. To determine the pH of the *stratum corneum*, a probe was chosen that can emit in both acidic and alkaline environments, but this emission is at different wavelengths. The resulting image indicates the luminescence in the acidic environment in blue-blue and the neutral-alkaline environment in orange. As a result, the colored images allow for calculating the average pH at different depths of the *stratum corneum*. It is calculated as the ratio of the area of blue areas to the orange areas.

The closer to the surface, the bluer. The calculated average pH value in the upper *stratum corneum* layers is slightly higher than in the hydrolipid mantle but still acidic — less than 7. In the middle of the *stratum corneum*, the pH is close to neutral. At the very depth, it becomes slightly alkaline.

The distribution of color in the *stratum corneum* is uneven. Blue acidic areas are separated from neutral orange areas. The *stratum corneum* consists of dense, almost waterless corneocytes, and inside them, pH is neutral. Free water in the *stratum corneum* is present in the intercellular space, and so this water, as clearly shown here, will be acidified. That is, even in the lowest layers of the *stratum corneum*, we still see areas with acidic pH, although there are fewer of them.

Under the *stratum corneum*, water is everywhere — both in the cells and intercellular space. The pH here is slightly alkaline, so we don't see individual cells, but we see uniform orange staining.

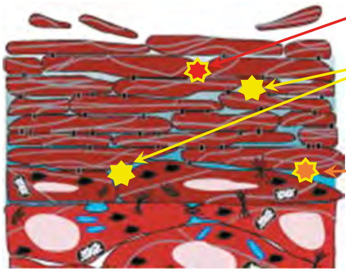

Figure II-2-2. Acid peel targets

cases, the skin peels as a result. So, alkaline preparations can also be used if our goal is to cause flaking. Remember how skin peels after washing with laundry soap? That's because the soap solution has an alkaline pH of 9–11. And yet alkaline peels are exotic today, but acidic peels are widespread and successfully used in different situations. In terms of safety, acidifying the surface pH is much better tolerated by the skin and safer than alkalizing it.

The more the pH gradient changes and the longer this condition lasts, the stronger the exfoliation. Therefore, the power of the acid peel depends on the formulation's pH and exposure time. The acids concentration is not critical: for example, a formulation with a total AHAs concentration of up to 70% and a pH of 5.5 does not exfoliate. On the contrary, a product with 30% and a pH of 1.5 causes noticeable scaling.

The burning sensation that appears some time after applying acid peels indicates that the acidification has gone beyond the *stratum corneum*. Nerve endings, distributed in the skin with high density, communicate with all skin cells — mast cells, endothelial cells, keratinocytes, Langerhans cells, and fibroblasts. In response to an external stimulus (e.g., a decrease in the pH of the intercellular space), nerve endings release neuropeptides such as the substance P or calcitonin gene-related peptide (CGRP) acting on neighboring cells. In turn, the cells release histamine and pro-inflammatory cytokines, which activate sensory nerve endings and trigger a signal transmission to the brain — this is the signal we perceive as burning. Histamine dilates blood vessels and provides blood flow to the problematic area to dissolve and eliminate irritants as quickly as possible (Choi J.E., Di Nardo A., 2018). If the acid action is not stopped, an inflammatory reaction (so-called **neurogenic inflammation**) is triggered in the epidermis (**Fig. II-2-3**).