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REVIEW

Considerations on the Use of Organic Substances in Chemical Peels: A Systematic Review

Soimita Emiliana Măgerusan[1], Gabriel Hancu[2*], Eleonora Mircia[3]

1. Department of Pharmaceutical Chemistry, Faculty of Pharmacy, George Emil Palade University of Medicine, Pharmacy, Science, and Technology of Targu Mures, Romania
2. George Emil Palade University of Medicine, Pharmacy, Science, and Technology of Targu Mures, Romania
3. Department of Pharmaceutical Industry and Management, Faculty of Pharmacy, George Emil Palade University of Medicine, Pharmacy, Science, and Technology of Targu Mures, Romania

Chemical peel is a dermato-cosmetic procedure used to destroy and remove, in a controlled manner and under the supervision of the specialists, the degraded parts of the skin, in order to allow acceleration of the skin regeneration process. Based on their depth of skin penetration chemical peels are classified into superficial, medium and deep peels. The substances used in the chemical peels differ from each other depending on the effective action depth. Different peel agents with an appropriate peel depth should be selected based on the problem to be treated, considering also the nature of skin pathology. To achieve the best results other factors, such as skin type and characteristics, region to be treated, safety issues, healing time, and patient adherence, should also be considered. The present review focuses on the particularities of the substances used in various peel types, highlighting recent advances in chemical peel technology and explaining suggested application of certain substances in different peel types.

Keywords: chemical peels, peel agents, alpha hydroxy acids, betha hydroxy acids, trichloracetic acid, phenols

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Introduction

Peeling is a dermato-cosmetic method used to remove dead cells from the skin surface in order to stimulate the function of the ones from the deeper layers of the skin. Most peeling techniques do not dramatically alter the architecture of the skin, because they mainly work at the level of the epidermis (superficial layer of the skin), but there are also more aggressive methods by which even the structure of the skin proteins can be altered [1].

Peels can be classified into two categories, depending on the mechanism of action: mechanical peels and chemical peels. Mechanical peels use the exfoliating action of the granules and abrasive particles contained in various creams or masks, which by easy and superficial massage removes the dead cells from the epidermis. Chemical peels are method of rejuvenation for facial care that involves exfoliation of the epidermis with the help of chemical substances; depending on the particularities and problems of the skin, it can be achieved using different substances [2].

Chemical peels can be classified in three categories [3,4]:

– superficial peels - the mildest form of peel, has the advantage of being able to be applied for all skin types; this method uses a weak acid (diluted acids, most often glycolic acid);
– moderate or medium peels - substances used in this type have the property of penetrating deeper into the skin than those used in superficial peels and cause the appearance of second degree burns (most often trichloroacetic acid peels);
– deep peels - it also determines the appearance of a second degree burns, but it differs through the substances that are used, in this case it is preferred the application of the solution based on phenols or higher concentration of trichloroacetic acid; this method is recommended only for people with serious dermatological problems and should only be performed by a dermatologist.

Superficial peels, which penetrate only the epidermis, can be used to improve treatment of different skin conditions, including acne, melasma, photodamage, dyschromias and actinic keratoses. Medium peels, that reach the papillary dermis, may be used for multiple solar keratoses, dyschromia, superficial scars, and pigmentation disorders. Deep peels, that affect reticular dermis, may be used for severe photoaging, deep wrinkles or scars [2,5].

The agent used in the chemical peels should be selected taking into account a series of variables such as application method, application area, contact time with the skin, skin type, medical history and patient's lifestyle and the formulation and concentration of the chemical agent. Among the factors that influence the penetration capacity of the tissues by chemical substances are the acidity of the peel agent, the number of layers applied, and the time given for the action, before the substance is neutralized. The depth of penetration is determined by the type, concentration and pH of the peel agent [6].

The mechanism of action of acids used in chemical peeling consists in the coagulation of dermal and epidermal proteins. In superficial peeling the necrosis occurs up to the level of the basal layer of the epidermis, while in me-

* Correspondence to: Gabriel Hancu
E-mail: gabriel.hancu@umfst.ro

dium and deep peeling the necrosis extends to the papillary and reticular dermis. The necrosis process is followed by re-epithelialization and improvement of the skin's appearance [5,7].

The current review presents the main chemical substances used in chemical peels used in cosmetics and aesthetics focusing on the peculiarities of substances used in various peeling types, highlighting recent developments in chemical peeling technology.

Alpha hydroxy acids (AHA)

AHA are a class of hydroxy-carboxylic acids in which a hydroxyl group is attached at the alpha position of the carboxyl group. AHAs are naturally occurring acids found in different fruit such as apples (malic acid), citrus (citric acid), grapes (tartaric acid), bitter almond (mandelic acid), sugar cane (glycolic acid) or milk (lactic acid) [8]. The chemical structures of AHA used in peels are presented in Figure 1.

Topical application of AHAs (in concentration higher than 25%) decreases the cohesion of corneocytes immediately above the granular layer, resulting in the stratum corneum detachment and layer desquamation from the first 24 hours of treatment. After application of an appropriate concentration of AHA on an aging skin, histological changes occur without edema or inflammation of the skin. Due to their stable molecular structure AHAs are not considered potential allergens, consequently their preliminary testing is not required before the peel operation [9].

The most commonly used acid in superficial peels is **glycolic acid** (2-hydroxyethanoic acid, hydroxyacetic acid). Glycolic acids have the smallest molecular size among all AHAs, it is a highly hydrophilic molecule and has the greatest bioavailability among AHAs as it penetrates the skin easily. It is usually used in concentrattions between 25% - 70% at a of pH 2-3; tolerance is generally good. The peel will be more intense with the increase of concentration and at lower pH values. Glycolic acid has a keratolytic, germinative layer and a fibroblast stimulating action. At low concentrations (<25%) produces only superficial exfoliation, at concentrations of 25-50% causes the discontinuity of keratinocytes, and at concentrations of 50-75% epidermolysis [10].

Glycolid acid peel is a minimally invasive cosmetic procedure commonly used for treatment of acne, photoaging and pigmentary disorders such as melasma. It can be used in a treatment every 3-4 weeks, in a total of 4 to 6 applications; based on the tolerance and results of previous applications, application time can be gradually increased. Glycolic acid reduces cellular cohesion at the lowest level of the stratum corneum, exfoliating dead cells, encouraging younger, brighter cells to the surface; this superficial exfoliation guarantees a reduction in comedonal acne, pore size, and acne lesions [9,10].

Lactic acid (2-hydroxypropanoic acid) is structurally almost identical to glycolic acid except for an additional methyl group. Lactic acid has a lower pH than glycolic acid, therefore lower concentrations are used to achieve an equal depth of keratocoagulation. Lactic acid peels are best suited for people with very sensitive skin that may not tolerate the slightly more aggressive glycolic acid peel [9].

Lactic acid improves the photo-aging of the skin, being effective in treating post-inflammatory hyperpigmentation lesions, melasma and solar lentigo. Lactic acid inhibits melanin synthesis by inhibiting tyrosinase activity. The treatment starts with low concentrations of lactic acid, the concentrations is increased progressively to avoid post-peel hyperpigmentation of the skin and irritation [11].

Other AHA including mandelic acid, are used less frequently in peels than glycolic acid or lactic acid.

Pyruvic acid (α-ketopropionic acid) is an alpha-keto-acid used as a medium chemical peel agent in inflammatory acne, moderate acne scars, greasy skin, actinic keratosis. It causes a slight peel of the corneal layer of the epidermis; the erythema disappears within a few minutes after the procedure and does not cause post-procedure hyperpigmentation spots. Pyruvic acid can be associated with lactic acid for the treatment of melasma [12].

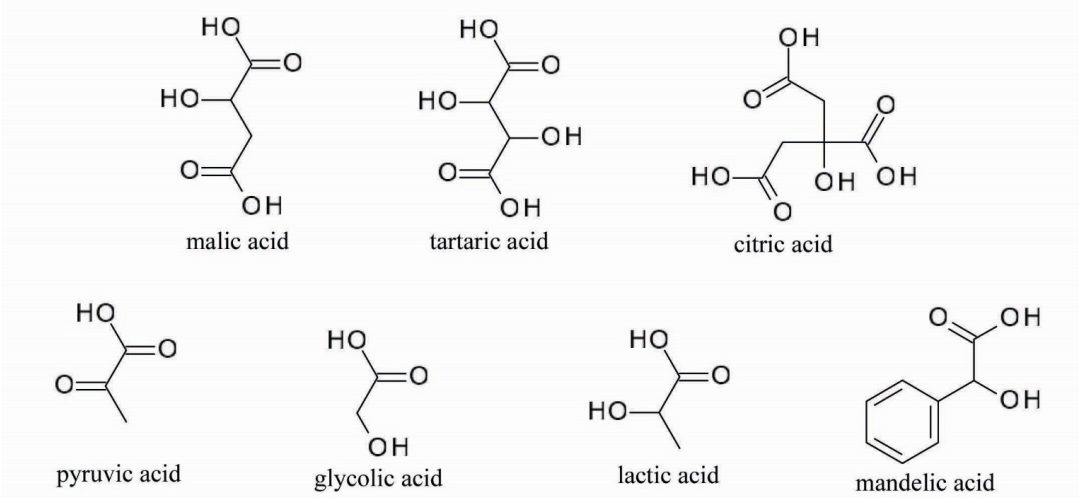

Fig. 1. Chemical structures of AHA used in chemical peels

AHA peels need neutralization to stop their action; this is achieved using usually sodium bicarbonate; however sodium hydroxide or ammonium salts solutions may also be used [9].

Beta hydroxy acids (BHA)

BHAs differs from AHAs by the presence of a hydroxyl group at the second carbon atom position (beta position).

Salicylic acid (2-hydroxybenzoic acid) is a naturally occurring aromatic hydroxyacid found in bark of the meaning white willow and in wintergreen leaves [13].

The chemical structure of salicylic acid is presented in Figure 2.

It is a lipophilic agent that produces the peel of the upper corneum layer and stimulates the basal cells and the subadiacent fibroblasts layer. Its antibacterial, anti-inflammatory, antifungal, and anticomedogenic properties can be explained as it prevents the synthesis of pantothenic acid, necessary for the life of microorganisms. It destroys intercellular lipids that are covalently bound to the cornified envelope surrounding cornified keratinocytes, thus desquamating the stratum corneum and activating basal keratinocytes and fibroblasts [13].

The therapeutic action of salicylic acid depends on the formulation, the solvent chosen in the preparation but also on the pH of the application site. Concentration formulas of 20% or 30% salicylic acid in ethanol, are used as a superficial peel agent. Superficial salicylic acid peels can be done at home with over the counter (OTC) products; stronger salicylic acid peels that penetrate more deeply should be performed by the dermatologist. It is applied for 3–5 minutes, causing a transient burning sensation; evaporation of the hydroethanolic solvent leaves a white precipitate which can be mistaken for frosting. In contrast to glycolic acid peels, salicylic acid peels do not induce frosting patterns or do not require neutralization [14].

It can be used in the treatment of skin damage due to sunburn, oily skin with large pores, comedogenic or inflammatory acne, rosaceous, epidermal melasma, postinflammatory hyperpigmentation. Salicylic acid peels are preferred to be used in comedonal and inflammatory acne, as well as for oily skin [15].

A lipophilic derivative of salicylic acid, lipohydroxy acid has been used in chemical peels. Lipohydroxy acid targets corneodesmosome protein structures to differentiate uniformly corneocytes; its higher lipophilicity results in a more complex mechanism of action in the epidermis and a higher keratolytic effect compared with salicylic acid. Lipohydroxy acid is used in concentrations of 5–10% and does not need neutralization [16].

Fig. 2. Chemical structures of salicylic acid

Due to the fact that BHAs are liposoluble and AHAs are hydrosoluble, it has been established that BHAs are more suited to the mixed, oily, normal skin that exhibits acne or has acne trends, also for skin with rosacea, while AHAs are more suitable for normal and dry skin. In recent years, more and more studies have emerged proving that AHAs have a beneficial effect on skin with excess sebum, in improving the appearance of post acne spots or caused by sun, post-acne scars, and in particular helps to smoothen color and texture skin [17].

A complex care routine for skin conditions is presented in Table I [18].

Trichloroacetic acid (TCA)

TCA is a structural analogue of acetic acid in which the hydrogen atoms in the methyl group have been replaced with chlorine atoms [19].

TCA precipitates epidermal proteins and causes destruction of upper dermis. Histologically, TCA is responsible for superficial coagulation of skin proteins and degradation of epidermis, followed by the rejuvenation of the epidermis and dermis with formation of new collagen storage and normalization of the elasticity of the tissue [19].

It is soluble in water and is used in concentration between 10-50%. The degree of the peel depends on the concentration of TCA and on the application time. Superficial TCA peel is performed at concentrations of 10–30%, medium-depth peel is performed at TCA concentrations of 35–50%, higher TCA concentrations (>50%) should be used with caution because of the risk of post-inflammatory hyperpigmentation and scarring. It may be used alone or as part of a combination peel, with other peel agents [20,21].

The superficial TCA peeling is used for the restoration of the skin appearance, for the treatment of wrinkles, in actinic keratosis and in the treatment of benign pigmented lesions. TCA is among the most used agents for treating scars caused by atrophic acne. Combinations of 40% TCA

Table I. Correlation between skin conditions and type of peels [18]

Skin condition	Recommended peel type
comedonal acne (black dots), all skin types	BHA
comedonal acne (white dots), all skin types	AHA
papulo pustulous acne, all skin types	AHA
cystic nodulous acne, all skin types	BHA
rosacea acne, all skin types	BHA
fine wrinkles, all skin types	AHA
spots and post acne scars, all skin types	AHA
superficial sunspots or melasma, all skin types	AHA
demodex, all skin types	BHA
eczema, all skin types	AHA
seborrheic dermatitis, all skin types	BHA
psoriasis, all skin types	BHA
improving skin texture, all complexion	AHA, BHA
skin color uniformity, all types of complexion	AHA

with 70% glycolic acid gel are used to reshape skin on the neck and chin, and combinations of 20% TCA with 5% ascorbic acid are effective in the treatment of melasma [22].

TCA cannot be neutralized and is not associated with allergic reactions or systemic toxicity. During TCA peels frosting can occur; frosting disappears in 20-30 minutes and is replaced by erythema, which can last 1-2 days. The redness can last for several days up to a week, and peels with TCA can be repeated after 2-6 weeks [21].

Retinoic acids

The family of retinoids comprises of vitamin A (retinol) and its natural derivatives such as retinoic acid, retinaldehyde, and retinyl esters, as well as many synthetic derivatives. Retinol is a 20-carbon molecule containing of a cyclohexenyl ring, a side chain with four double bonds (all in trans configuration forms), and an alcohol end group, hence the term all-trans-retinol. The oxidation of the alcohol end group of retinol results in the formation of an aldehyde (all-trans retinaldehyde or retinal), that can be further oxidized to a carboxylic acid (all-trans retinoic acid or tretinoin) [23].

Tretinoin (all trans-retinoic acid) is a retinoic acid derivative used in superficial chemical peels. Tretinoin has been shown to improve photoaged skin. A 1% tretinoin peel proved to be as effective as 70% glycolic acid in the reduction of the pigmentation in melasma in dark-skinned patients, being also less irritating and therefore better tolerated. There are still question marks about the advantage of highly concentrated tretinoin peels (5-10%) versus its continuous use at lower concentrations (1%) [24].

The chemical structure of the main retinoic acid derivatives are presented in Figure 3.

Phenols

Phenol (hydroxybenzene, carbolic acid) is an aggressive peel agent used usually in deep peels. Its use is limited by its high toxicity; it is strongly caustic, coagulates albumin and destroys mucous membranes and skin; it is recommended to be handled with rubber gloves [25].

Phenol peel effects vary depending on its strength and the surface area to which it is being applied. Phenol induces rapid and irreversible denaturation and coagulation of epidermal keratin and proteins at concentrations above 80%, this results in the creation of a barrier that prevents the peel agent from penetrating into the deep dermis. A 50% phenol solution acts as a keratolytic agent; disrupting sulfur bridges and allowing further penetration into the dermis, causing greater destruction and systemic absorption. Systemic absorption via the skin into the systemic circulation may cause serious adverse effects including renal failure and hepatotoxicity, cardiac arrhythmias, making it a potentially dangerous agent in inexperienced hands [26].

Phenol peel is used to treat facial wrinkles, skin spots caused by pregnancy, birth control pills, viral illnesses, sun exposure including precancerous skin conditions. Another disadvantage is represented by the fact that it stains the treated areas of the skin used for peel; consequently, is used for the peel of the whole face or on limited areas of the face where the contrast with the untreated areas is not so obvious. Phenol peels are used primarily on the face, since it can cause scarring if used on the neck [26].

Resorcinol (m-dihydroxy benzene, 1,3-dihydroxi benzene) is a phenol derivative, the isomer of catechol and hydroquinone.

It is a bactericidal, reducing agent with keratolytic properties; by stimulating prostaglandin E_2 formation and disrupting the hydrogen bonds of keratin. Resorcinol is used in concentrations of 10–50% for chemical peel in the treatment of acne, acne scars, epidermal melasma, mild photoaging and freckles. Side effects linked with resorcinol peels include allergic dermatitis, irritant contact dermatitis and post-inflammatory hyperpigmentation [27].

Hydroquinone (p-dihydroxy benzene, 1,3-dihydroxi benzene) is usually used as topical depigmenting agent effectively clearing melanin pigments in melasma. It can be used to treat skin condition associated with hyperpigmentation [28].

The chemical structures of phenols used in peels are presented in Figure 4.

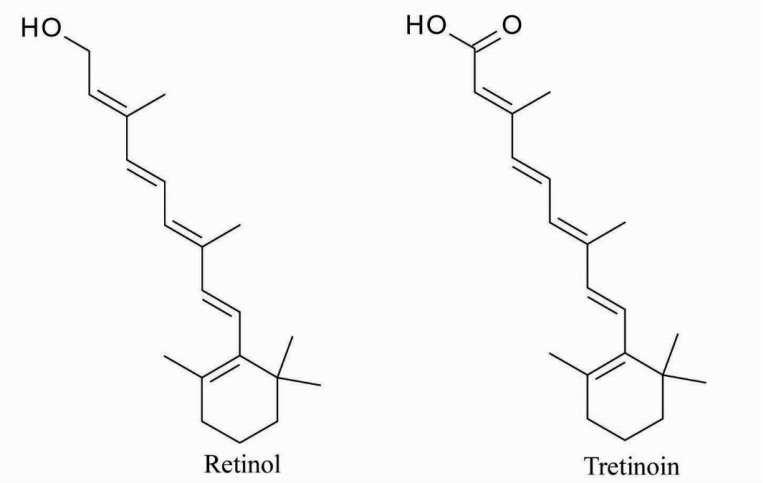

Fig. 3. Chemical structures of retinoic acids derivatives

Several other composed phenol formulas have been used for deep chemical peels. These formulas consist of phenol in varying concentrations together with other ingredients such as croton oil (Baker-Gordon phenol peel, Hetter phenol-croton oil peel) [29].

In practice more and more emphasis is placed on combining various peel agents, with advantages related with the decrease of the complication and risks of the peel by using lower concentration of substances, accelaration of the tissue regeneration and subsecent time for recovery and extension of the application range.

Jessner solution

The most frequently used peel combination formula is Jessner solution. Jessner solution contain of a mixture of 14 g salicylic acid, 14 g resorcinol, 14 mL lactic acid 85% in 95% ethanol q.s. Modified Jessner solution which do not contain resorcinol (considered to be responsible for side effects such as irritant and allergic contact dermatitis and skin discoloration) are also used. It is a clear, amber-colored photo sensitive solution that needs to be kept in a brown bottle to prevent oxidation [30].

Jessner solution is used in peels to treat acne, melasma, lentigines, post-inflammatory hyperpigmentation, freckles, and photodamage. Application of Jessner leads to loss of corneocyte cohesion and induces intercellular and intracellular edema [29].

Jessner solution is generally applied in two coats, additional application increases the depth of the peel. It does not require neutralization. After application mild erythema and patchy frosting develops. It is also used as a preparatory peel to enhance the penetration before a peel with TCA [31].

The factors affecting the depth of the peel, and thus its effects on the skin, include the properties of the chemical agent used (e.g., concentration and pH), the application technique, and the patient's skin condition and sensitivity. Also, the depth of the peel is cumulative and dose-dependent; as a monolayer of application can lead to a superficial peel, while subsequent multiple layers application will result in an additive deeper peel [32].

A classification of the chemical peel agents based on the depth of penetration is presented in Table II [33].

Recently, the mechanism and techniques used in peels suffered a slight change, as lasers are more and more frequently used in deep peels due to their enhanced ablative depth modulation and relative lack of adverse effects and toxicity. However, the popularity of superficial peels also increased in popularity, demonstrated by the large number of OTC cosmetics on the market [34].

Statistically currently chemical peels are among the most frequently performed noninvasive cosmetic procedures together with botulinum toxins and soft tissue fillers [35].

Conclusions

Chemical peeling is a slightly invasive dermatoesthetique procedure that consists in the application of chemical substances on the skin that follows the controlled destruction of the skin layers, having the effect of peeling the skin to varying degrees. In this way, dead cells are removed from the superficial layers of the skin and at the same time cells from the deep layers are stimulated to regenerate and produce collagen and elastin.

Although there can be slight variation between the categories of peel agents and their desired cosmetic effects, a chemical peel ultimate purpose is to enhance the clinical appearance of the skin by minimizing the quantity and consistency of wrinkles and acne scars, decreasing inflammatory acne lesions, enhancing dyspigmentation and giving an overall more youthful look.

Chemical peels are non-invasive intervention with the ability to solve a personalized problem of skin imperfection,

Fig. 4. Chemical structures of phenols used in chemical peels

Table II. Peeling agents used in different peel types [33]

Peel type	Peel agent	Depth of penetration
Superficial	AHA - glycolic acid (30–50%), lactic acid (10–30% mandelic acid (40%) BHA - salicylic acid (30%) pyruvic acid (50%) resorcinol (25-50%) Jessner solution (3-7 coats) TCA 10-35 % (1 coat)	superficial/stratum corneum exfoliation/epidermal necrosis
Medium	BHA – salycilic acid (>30%) AHA - glycolic acid (>70%) – with or without pretreatment Jessner solution TCA (30-50%) – with or without pretreatment Jessner solution TCA 35% + glycolic acid 70%	medium depth/papillary dermal necrosis
Deep	TCA (>50%) - pretreatment Jessner solution Phenol 88% Baker-Gordon phenol peel (50–55% phenol)	deep/reticular dermal necrosis

to allow the choice of the level of epidermal penetration: superficial, medium or deep. Regarding the characteristics of the skin, one can choose one of the three variants and the peel agent. When used for the appropriate indication by professionals, noninvasive chemical peel solutions demonstrated very good clinical efficiency in improving skin tone and texture and are cost-effective solutions compared to invasive procedures.

Authors' contributions

Soimita Emiliana Măgerusan (Conceptualization; Data curation; Formal analysis; Methodology; Project administration; Resources; Writing – original draft; Writing – review & editing)

Gabriel Hancu, associate professor (Conceptualization; Data curation; Formal analysis; Methodology; Project administration; Resources; Supervision; Writing – original draft; Writing – review & editing)

Eleonora Mircia, associate professor (Conceptualization; Data curation; Formal analysis; Investigation; Methodology; Resources; Supervision; Writing – original draft; Writing – review & editing)

Conflict of interest

None to declare.

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