Contents

tion enhancers in the micro-emulsion's oil phase, such as oleic acid, or by the use of surfactants. Their clear appearance and ease of application increases their desirability and use in many cosmeceuticals, including moisturizers, sunscreen preparations, tanning products, antiaging products, antiperspirants, deodorants, hair care and coloring products, and perfumes. A common concern related to micro-emulsion use for topical delivery is their potential side effects, mainly skin irritation potential and comedogenic effects. These side effects are generally associated with exposure time and the composition and concentration of components, especially of surfactants, and components of the oil phase.

Nano-emulsions are emulsions with droplets smaller than 100 nm, comparable to the size of micro-emulsions despite what the name implies [22]. Nano-emulsions present the advantage of being formed with smaller amounts of surfactants, and thus lower skin irritation potential [23]. The preparation of stable nano-emulsions generally requires expensive, high-energy input methods. Nano-emulsions are kinetically, not thermodynamically, stable [24]. Their instability leads to a more favorable use of other nano-sized delivery systems like nanosomes or solid lipid nanoparticles (SLNs), which will be discussed later. Nano-emulsions are used for transcutaneous delivery of multiple agents, including gamma tocopherol, caffeine, and plasmid DNA [25–27].

Vesicular Lipid-Based Systems

Over the past few years, vesicular-based systems have been increasingly used as a compelling means of transcutaneous delivery of various therapeutic agents. A vesicular-based system consists of a concentric lamellar structure with an aqueous core surrounded by a phospholipid bilayer [28]. These systems provide multiple opportunities for the entrapment of hydrophilic, lipophilic, and amphiphilic drugs. Mechanisms of drug transport involve improving drug solubility, drug partitioning into the skin, and fluidizing SC lipids

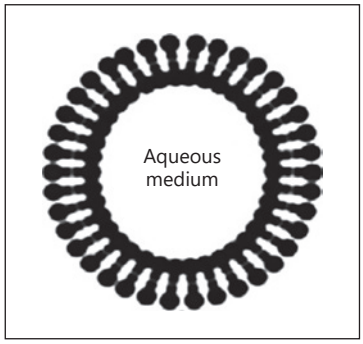

Fig. 2. Structure of a liposome.

[29]. Vesicular-based systems consist of three main carriers: liposomes, transfersomes (ultra-deformable liposomes), and ethosomes [30] (Table 1).

Liposomes

The first generation of vesicular-based systems are liposomes, which were first described by Mezei and Gulasekharam [31] in 1980. A liposome is formed by a lipid bilayer surrounding an aqueous solution (Fig. 2) and can range in size between 200 and 800 nm [29, 32]. Drug delivery using these carriers is mainly limited by their rigidity and size, which can impede SC penetration. Liposomes more than 600 nm in size do not penetrate deeply and remain in the SC. Their advantages lie in the wide variety of drugs that can be incorporated as well as their biocompatibility with natural phospholipids. Examples of drugs delivered throughout the skin using liposomes are curcumin and retinoic acid [33–35]. Furthermore, liposomes have been utilized to deliver siRNA through the skin and impact protein expression at basal keratinocytes [36].

Transfersomes

The need for smaller, more elastic carriers led to the development of the second generation of vesicular-based lipid carriers, transferosomes, also termed ultra-deformable liposomes [37]. In 1992,

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Cevc and Blume [38] introduced the transfersomes, which resemble liposomes in morphology but are more lipophilic, smaller than 300 nm, and are at least one order of magnitude more elastic than liposomes. Furthermore, when compared to liposomes, transfersomes contain one or more edge-activator substance(s), surfactants being the most commonly used edge-activators. Edge-activators typically used for ultra-deformable liposome preparation include sodium cholate, sodium deoxycholate, Span 60, Span 65, Span 80, Tween 20, Tween 60, Tween 80, and dipotassium glycyrrhizinate [37]. There are 2 major proposed mechanisms of skin delivery via ultra-deformable liposomes [37, 39]. The first mechanism proposes that the deformable nature of the intact vesicles contributes to their entry into the SC. The second mechanism proposes that vesicles act as penetration enhancers, whereby vesicles modify the intercellular lipids of the SC. Because their transport across the skin is driven by a hydration gradient, occlusive application can compromise the action of the deformable vesicles by eliminating the gradient force. One disadvantage of these vesicles corresponds to the difficulty in loading hydrophobic drugs into the vesicles without compromising their deformability and elastic properties [39].

Ethosomes

Godin and Touitou [40] developed the third generation of liposomes, called ethosomes. An ethosome is composed of an aqueous core, phospholipid bilayer, and ethanol (20–45%). The incorporation of high ethanol concentration, which differentiates ethosomes from other vesicular-based carriers, confers a negative charge to the liposomes which causes the vesicular size to decrease to the nanometer range, thus enhancing their skin permeation capacity. They also have higher elasticity, typically 10–30 times higher than conventional liposomes [40, 41]. Unlike transfersomes, ethosomes are able to improve the skin delivery of drugs both under occlusive and nonocclusive conditions. The addition of ethanol in ethosomes may contribute to their superior delivery properties, which can lead to the systemic absorption of drugs encapsulated within ethosomes [41]. The potential of ethosomes for irritation and systemic absorption in addition to their long-term safety needs further exploration. Ethosomal delivery systems dramatically enhance skin permeation of minoxidil and have been used in the delivery of hyaluronic acid [42–44].

Other Emerging Lipid-Based Vesicles

Niosomes are nonionic unilamellar or multilamellar vesicles in which the active ingredient is encapsulated. They have improved the stability and availability of active ingredients as well as skin penetration compared to liposomes. Examples of drugs delivered using niosomes are minoxidil and ellagic acid [44]. The synergistic effects of two antioxidants, α-tocopherol and curcumin, were demonstrated using a niosomal delivery system [45].

Ultrasomes are liposomes encapsulating a UV-endonuclease enzyme [46]. They help repair UV-induced DNA damage and inhibit the expression of pro-inflammatory cytokines. Similarly, photosomes help repair DNA damage by encapsulating a light-activated enzyme (photolyase) in a liposomal structure and are thus included in certain sunscreen products.

Lipid Particulate Carrier Systems

Lipid particulate carrier systems have attracted researchers and gained popularity over other delivery systems in recent years because of the availability of nontoxic and bio-compatible lipid ingredients [47]. Lipid particulate systems typically include micro-capsules, micro-sponges, and lipid nanoparticles, such as SLNs and nanostructured lipid carriers (NLCs) [47].

Micro-Capsules

The use of micro-capsules in cosmeceutical products has gained more interest in recent years due

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ing hyaluronic acid, which is also used as a humectant in cosmeceutical preparations. Other common humectants include glycerin, sodium lactate, urea, propylene glycol, sorbitol, pyrrolidone carboxylic acid, gelatin, vitamins, and some proteins [4, 5].

Finally, emolliency is an important concept in cosmeceutical efficacy. Emollients smooth down desquamating corneocytes to make the skin surface appear smooth and feel soft, which are very important consumer-perceived cosmeceutical benefits [6]. In addition, some emollients are also occlusive moisturizers. Important to consumer satisfaction with a moisturizing product since smooth skin is expected following application, even though emolliency may not necessarily correlate with decreased TEWL. Emollients function by filling the spaces between the desquamating skin scale with oil droplets, but their effect is only temporary. Commonly used emollients include propylene glycol, isopropyl isostearate, octyl stearate, and isopropyl myristate [7].

Most cosmeceutical moisturizers consist of water, lipids, emulsifiers, preservatives, fragrance, color, and specialty additives. Most cosmeceuticals are 60–80% water with the water functioning as a diluent, rapidly evaporating after application. Emulsifiers are generally detergents in concentrations of 0.5% or less, keeping the lipids emulsified in the water to form one continuous phase. This then means the specialty additives become the differentiating factor between various cosmeceutical moisturizer products. In summary, a cosmeceutical moisturizer formulation must increase the water content of the skin (moisturization) and make the skin feel smooth and soft (emolliency).

Noninvasive Testing of Cosmeceutical Moisturizer Efficacy

Most cosmeceuticals are evaluated prior to marketing to be sure they meet formulation efficacy goals. Since invasive biopsy analyses are not appropriate, given that drug-like effects could be demonstrated, cosmeceuticals are tested with noninvasive methods. These noninvasive methods include regression analysis, profilometry, squametry, in vivo image analysis, corneometry, and evaporimetry [8].

Regression analysis is an important method to determine if a moisturizer can produce benefits even after application has been discontinued. A good cosmeceutical moisturizer will maintain some benefits 48 h after the product was applied. Most regression studies will have the subjects apply the facial cosmeceutical for 2–4 weeks followed by discontinuation. The skin will be evaluated at the end of the study period; subjects will discontinue application, return to the research center 48 h after the last application, and undergo evaluation [9]. This method is particularly valuable since the efficacy of all moisturizers is excellent immediately following application, but true effectiveness can only be assessed based on the longevity of benefits [10].

The minimization of fine lines and wrinkles is a commonly purported cosmeceutical benefit. One noninvasive method used to document wrinkle reduction is profilometry, which involves the analysis of silicone replicas of the skin surface with scanning laser imaging. The unpolymerized silicone, which is the same as dental impression material, is mixed with the catalyst. The silicone is placed over the skin surface to create a negative replica of the skin texture. Analysis of these replicas before and after application of the cosmeceutical can determine the ability of the product to minimize wrinkles and support wrinkle reduction claims [11].

Many cosmeceutical moisturizers claim to smooth the skin surface or uncover younger skin through exfoliation. Exfoliation removes nonliving corneocytes from the skin surface, which is a cosmetic effect, by using ingredients that digest the intercellular bonds. Ingredients capable of inducing exfoliation include glycolic, lactic, malic, and salicylic acids. While the appearance of exfoliated

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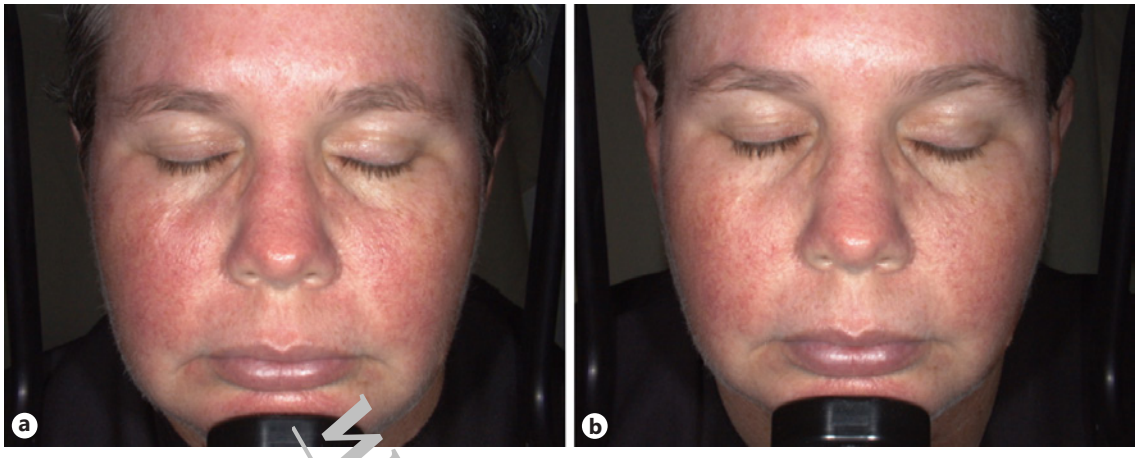

Fig. 1. Before (**a**) and after (**b**) images post-application of a cosmeceutical designed to minimize facial redness.

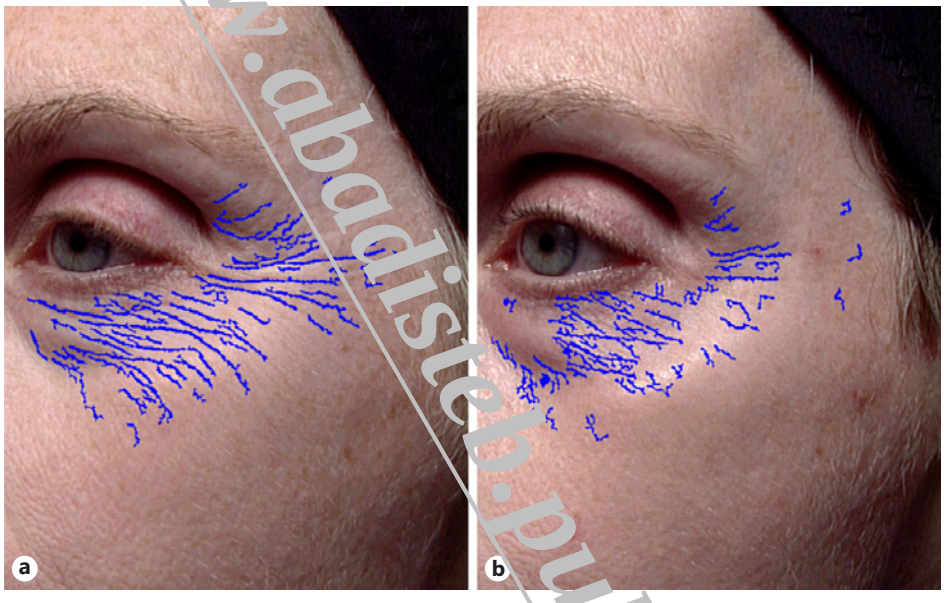

Fig. 2. Before (**a**) and after (**b**) facial images to assess the efficacy of a cosmeceutical designed to minimize fine lines/wrinkles utilizing digital image analysis.

computer algorithm for pattern recognition. More pores have been highlighted in the before (Fig. 3a) than the after (Fig. 3b) image. Will the consumer be able to perceive the pore reduction? This is the challenge when using computer assessment to evaluate cosmeceutical efficacy.

Developing a Plan for Cosmeceutical Evaluation

No cosmeceutical can deliver all skin benefits; thus it is important to determine the goals of the formulation. The conceptualization of the cosme-

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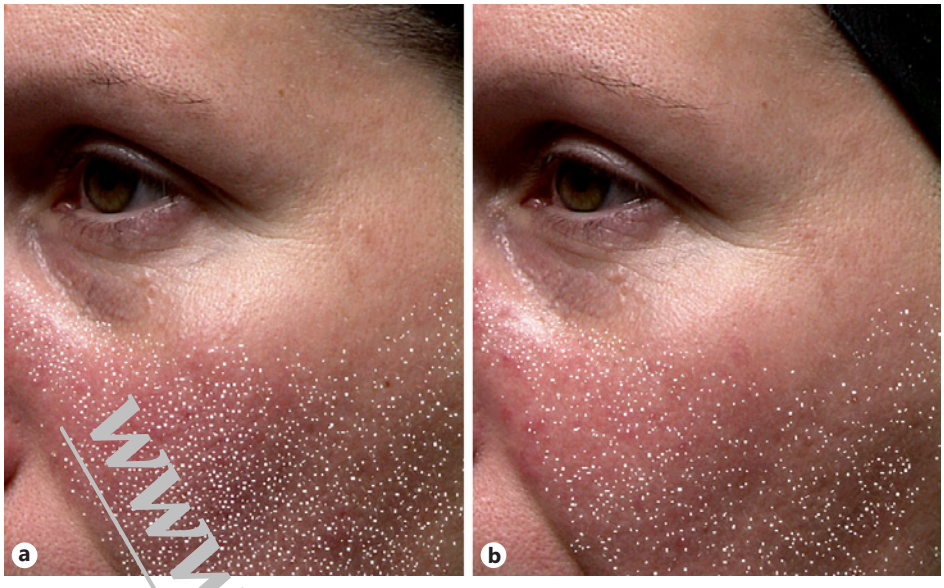

Fig. 3. Before (**a**) and after (**b**) facial images to assess the efficacy of a cosmeceutical designed to minimize pores utilizing digital image analysis.

ceutical should address the needs of aging skin (Table 1). Sometimes it is better to elucidate the desired benefits of the cosmeceutical first and then fit the formulation to claims rather than the claims to the formulation. However, realistic benefits are important, or the consumer will purchase the cosmeceutical once, but not again. This is the biggest reason for cosmeceutical failure in the marketplace. It is also the biggest reason why cosmeceutical formulations enter and exit the marketplace with great rapidity, promising that the new formulation works better, faster, and with more dramatic results.

If the cosmeceutical is designed to address lines and wrinkles of the face, the formulator should target which lines and wrinkles will be improved and then fit available ingredients to the goal. It is also possible that some wrinkles of the face cannot be addressed with a topical product, in which case more minor lines should be selected for minimization. Skin color and dyspigmentation problems may be addressed alone or in combination with wrinkles and folds. Cosmetic retinoids, such as retinol, can improve all of these facial aging issues, but care must be taken not to drive the concentration too high so as to induce irritation. Skin irritation can be tolerated in prescription retinoid use under the direction of a dermatologist, but irritation must be avoided at all cost in cosmetic formulation. Similarly, brown skin dyspigmentation can be treated with skin lightening cosmeceuticals containing hydroquinone.

Table 1. Needs of aging skin

1.	Fine lines
2.	Wrinkles: dynamic and static
3.	Folds
4.	Skin color
5.	Dyspigmentation
6.	Texture

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Cosmeceutical Ingredient Challenges

No evaluation of cosmeceuticals is complete without a brief discussion of ingredient challenges. Cosmeceutical formulation involves the careful selection of ingredients to produce a safe, elegant, efficacious product suitable for patient purchase [17]. Many considerations go into a final formulation including moisture barrier effects, pH, lubricating action, soothing effects, osmotic effects, emolliency, and percutaneous absorption [18]. Some of the more controversial ingredients that go into cosmeceuticals include preservatives, herbal additives, and biologic additives.

Preservatives

Preservatives are perhaps the most controversial of all cosmeceutical ingredients. All currently available preservatives are made synthetically as no totally natural preservative blend has been created to date. No cosmeceutical can be sold commercially without refrigeration devoid of preservatives. However, preservatives have been blamed for everything from breast cancer to obesity to environmental damage. Without preservatives, the occlusive and emollient lipids in cosmeceutical formulations would rapidly oxidize, rendering the cream rancid, or bacterial contamination would render the water-soluble ingredients unsafe. Preservatives are the second most common allergenic group of substances found in cosmeceuticals behind fragrances [19]. However, the number of cases of irritant and allergic contact dermatitis are indeed small compared with the two necessary functions preservatives perform in cosmetics: spoilage prevention prior to purchase and prevention of contamination after purchase [20, 21]. Paraben esters are the most popular preservatives used in cosmetics as their sensitization and irritation potential is low when applied to healthy skin [22]. They are usually found in concentrations of 0.5% or less in the USA. Some of the "natural" cosmeceuticals use essential oils and fragrances with antimicrobial capabilities, such as oil of clove, cinnamon, eucalyptus, rose, lavender, lemon, thyme, rosemary, and sandalwood [23].

Herbal Additives

Herbal additives possess tremendous consumer appeal due to their "natural" derivation, even though herbicide and heavy metal contamination is a problem. Botanical ingredients must be carefully sourced for purity or formulation problems will ensue [24]. The addition of herbals makes the distinction between a standard mass-produced body moisturizer and a boutique cosmeceutical moisturizer. Plant additives are purchased from large manufacturers and typically added to the cosmeceutical at the end of processing either as a liquid or powder. The plant material may color and scent the final product, but also add skin benefits [25].

Herbal additives may take several forms, including: hydroglycolic extracts, essential oils, and whole plant extracts [26]. Hydroglycolic extracts, such as aloe vera, are used in concentrations of 3–10% and are a combination of propylene glycol and water, yielding water-soluble constituents, but not oil-soluble aromatic fragrances [27]. Essential oils, such as avocado oil, sesame oil, and tea tree oil, are used in concentrations of 2–5% [28]. Whole plant extracts, also known as aromaphytes, are used at 5–20% concentration and manufactured by double extraction containing all the constituents of the plant. In cosmeceuticals, herbal additives are sometimes added for their antioxidant capabilities, but efficacy must be assessed based on the quality, concentration, and composition of the herbal ingredient.

Biologic Additives

Biological additives are also found in cosmeceuticals and are derived from the extracts and hydrolysates of glands and tissues of animals of different species. Biologics can be obtained as aqueous, hydroglyceric, hydroalcoholic, hydroglycolic, and oily extracts of animal-derived products. Commonly used cosmeceutical biological additives in-

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clude collagen, elastin, hyaluronic acid, keratin, placenta, blood derivatives, and stem cells.

Collagen, a large molecule composed of three twisted alpha helical peptide chains, is a biological additive used in some cosmeceutical moisturizers. Collagen is usually obtained from shredded calf skin that is carefully handled to eliminate denaturation.

Elastin, a structural component of the dermis responsible for the ability of the skin to regain its original configuration following stretching and other deformation, is obtained from bovine neck ligaments. Elastin, usually added as a hydrolysate, is a clear yellow liquid. While the addition of collagen and elastin to a cosmeceutical moisturizer might be presumed to thicken skin and increase elasticity, these ingredients actually function as humectants to improve the water-holding capacity of the skin [29]. Part of evaluating cosmeceutical efficacy is to determine the true value of a biologic additive.

Conclusion

This chapter has presented some of the important considerations regarding cosmeceutical efficacy. The cosmeceutical concept has great consumer appeal because the idea of putting a cream on an aging face to make it look young again is enticing. While Ponce de Leon was actually pursuing a cosmeceutical concept when looking for the fountain of youth, he was never successful in his quest. Most consumers will not be successful in their quest either. Nevertheless, great advancements have been made in cosmeceutical formulations and understanding how to evaluate their efficacy is important.

Conflict of Interest Statement

The author has no financial, commercial, or other relationships to declare as a possible conflict of interest.

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Author Contributions

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