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Review

Strategic Approaches in Formulation Development for Atopic Dermatitis

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Abstract: Atopic dermatitis (AD) is the most common chronic skin disease, significantly impacting patients' quality of life. One of the most effective management approaches for AD involves addressing the defective skin barrier by urging AD patients to regularly use suitable moisturizers. Therapeutic moisturizers designed for AD are precisely formulated with ingredients targeting critical and often early symptoms of AD (e.g., itch, inflammation, damaged skin barrier). Dermo-cosmetic products, which are rich in moisturizing and emollient agents contributing to recovery as well as strengthening the skin barrier, have proven to be excellent adjuncts in AD treatment. There are various galenic forms of dermo-cosmetics, such as lotions, gels, creams, foams, and sprays, requiring a rationale in choosing ingredients for the product formulation and development. In addition, the role of moisturizer and emollient therapy to address skin dryness linked to dermatological conditions is hugely dependent on varying chemistry and morphology in the deeper regions of the skin. There are also limits to the efficacy of treatments, corticosteroid side effects, and product sensory appeal, which may decrease patient acceptance and compliance. The objective of this review is thus to offer a comprehensive overview of the critical aspects involved in the development of cosmetic vehicles, as well as a detailed examination of the primary ingredients used in formulations for AD.

Keywords: atopic dermatitis; topical formulations; vehicle; moisturizer; dermo-cosmetic

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1. Introduction

Studies have demonstrated that the skin acts as a vital interface between the body and external factors, providing major functions to support and protect the body against different physical and chemical risks [1–4]. The development of skin barrier abnormalities and immunological diseases is influenced by a complex combination of hereditary and environmental components [1]. Atopic dermatitis (AD) is considered a prime example of a chronic skin condition and has a complex pathophysiology [5]. The disease can provoke visible irritation (redness), itchiness, and discomfort on the skin [6]. It is also connected with other atopic conditions, including food allergies, allergic rhinitis, and asthma [7–10]. AD can affect individuals of all ages and is the most prevalent skin disease among children, affecting approximately 15–20% of infants and young children and 2–3% of the general population [5,11–13]. The disease typically begins by age 5, and early diagnosis and management are crucial to prevent complications and enhance quality of life [12,14,15]. Previously, individuals with AD were often described as having eczema, though "eczema" is a broader term encompassing various skin inflammatory conditions [8,16–18].

The objectives of AD treatment are to alleviate itching and burning, restore and maintain skin barrier function, reduce inflammation, interrupt the itch-scratch cycle, and address exter-

nal triggers and secondary infections that may exacerbate the condition [7,19,20]. One of the main treatments for AD includes applications of emollients and skin care products [20,21]. In randomized, double-blind studies involving healthy skin, specific emollients have been shown to enhance water gradients and improve hydration of the stratum corneum (SC). These emollients contain ingredients that can either replace or boost epidermal lipogenesis, thereby strengthening the SC barrier function [22,23]. Additionally, emollients enhance skin hydration and alleviate symptoms such as stinging and itching, as well as serve as a barrier against potential irritants [24,25].

Furthermore, dermo-cosmetic products have proven to be excellent adjuncts in the treatment of AD since they do not contain corticosteroids in their composition but offer a formulation, rich in moisturizing and emollient agents that can contribute to the recovery and strengthening of the skin barrier [26]. This work aims to review and evaluate different topical vehicles often used for drug delivery, focusing on their formulations, and intended impact on the skin, in order to enhance understanding of their qualities and facilitate informed decision-making for the treatment of AD.

2. Rationale for the Development of a Topical Vehicle for Drug Delivery

Considered as a delivery system to carry cosmetic or pharmaceutical active ingredients (APIs), a topical vehicle may also possess emollient properties that enhance skin hydration [27–30] and significantly affect the bioavailability of the active substances [29,31]. Topical therapeutic products are widely used to manage various dermatological conditions such as eczema, psoriasis, or xerosis [7,32]. In general, a final topical drug product is made by combining one or more APIs with different inactive ingredients that form the vehicle [31]. A vehicle can be a cream, lotion, gel, or ointment supporting the delivery of APIs across the stratum corneum (SC) into deeper regions, named the epidermis and dermis, of the skin [6]. The vehicle solubilizes insoluble drugs and provides a means for APIs to be applied evenly, remain protected, and reach unreachable strata of the skin. A vehicle is, thus, as important as the APIs because they both define the pivotal sensory characteristics favoring the adherence of treatment for skin conditions to the topical formulation [33]. There are different intrinsic and extrinsic factors that should be considered in structuring a vehicle, such as the solubility of the APIs in the formulation, the release form of the APIs at the time of application, the stability of the APIs, the vehicle itself (e.g., selection of excipients and formulation design), the hydration capacity of the SC, skin type, the application area, and importantly, the patient's preference for the vehicle [6,34]. Even though APIs are not present, applying a topical formulation to the skin may provide either eased (positive) or discomfortable (negative) feelings instantly, and the effects may persist for hours. Moreover, the commencement of clinical effects is usually gradual; hence, a well-tolerated formulation can contribute largely to patient compliance and the clinical success of topical drug products [35]. Additionally, assessing the current condition of the skin under environmental aspects such as ethnicity, gender, age, location, and disease status would be helpful in choosing a vehicle with good design quality [36].

In the context of AD, skin dryness and impaired barrier function (often with visible redness) are hallmarks of the skin diseases favoring invasion of microorganisms, allergens, and irritants [37]. The research of Danby et al. [32] indicated that so-called inert excipients within a topical formulation could induce molecular changes in the skin, promoting barrier repair, bolstering innate immune defenses, or offering therapeutic benefits for AD patients. The interaction between the vehicle and skin barrier is also crucial to addressing the condition's development and progression [6]. Therefore, a strategy is necessary in the formulation and development of vehicles that can calm and protect the skin while maintaining its pleasant sensory characteristics [5,38]. Many topical dosage forms contain ingredients with high emollient power that act as active ingredients on their own and have therapeutic potential for the product [32,39]. Proksch and Lachapelle [38] reported that the application of lipids, physiological lipids, and humectants could play a role in restoring

the lipid lamellae, improving skin biophysical properties such as skin hydration and skin elasticity, and thus reducing itching.

3. Key Vehicle Forms for Topical Drug Therapy

Key topical vehicle formulations, made from different excipients and ratios, can be distinguished based on their physical states such as liquids and semisolids [6,40]. Table 1 presents some main characteristics of the most common vehicles used in topical formulations, suggested areas of product application, and their possible effects.

3.1. Creams

As some of the most common topical semisolid dosage forms for dermatological applications, creams are characterized as emulsion system, consisting of a lipophilic phase with lipophilic (e.g., vegetable or mineral oils, alcohols, fatty acids, esters, and waxes) and an aqueous phase, combined through the action of emulsifiers [41,42]. According to the continuous phase (oily or aqueous), creams can be classified as water-in-oil (W/O) or oil-in-water (O/W) emulsions [43]. The O/W emulsions are particularly suitable for delivering water-soluble active substances, as their external phase exhibits hydrophilic properties. Conversely, W/O emulsions are optimal for lipid-soluble active substances, given that their external phase possesses lipophilic characteristics [44]. These kinds of emulsions exhibit no obstruction to heat dissipation owing to their miscibility with surface exudation. Cream emulsions impart a non-greasy sensation, a factor of paramount importance for certain patients [45,46].

3.2. Lotions

Lotions have a formulation structure similar to creams but may contain more than 50% water in their composition, resulting in greater fluidity [47]. Assessments of physical critical quality attributes (CQAs) such as rheological properties are often applied to discriminate cream and lotion products [31,48]. Due to their high-water content, lotions promote a pleasant cooling effect. Lotions are highly suitable for treating exudative dermatoses. Additionally, they can be applied easily in regions with hair like the scalp and demonstrate rapid spreadability [44].

Table 1. Characteristics of the most common topical vehicles.

Topical Formulations	Aspect	Application Area	Effect	Key Features
Creams [41,45]	semisolid emulsion	face and localized areas	moisturizer and a non-greasy sensation	no obstruction to heat dissipation
Lotions [44]	fluid emulsion	skin, body, and scalp	cooling effect	easy application
Ointments [43]	oily	specific area	occlusive effect	one phase vehicle
Gels [6,43]	thick gel	oily skin or areas with hair	film-like effect on the skin	easy removal
Foam [6,49]	aerated foam	sensitive skin	pleasant effect	reaches large areas
Spray [6,50]	solution aerosol	skin body, and scalp	cooling sensation	reaches large areas, may cause a burning and stinging sensation
Shampoo/Soap [41]	solid or liquid	skin, scalp	cleaning effect	reaches large areas
Paste [41]	semisolid, stiff consistency	skin, oral cavity, mucous membrane	occlusive and protective actions	skin protection and absorb secretions

3.3. Ointments

Ointments usually have a single phase, comprising lipophilic ingredients (e.g., soft paraffin), which could form an occlusive layer over the skin to prevent heat and water loss. Ointments may contain other ingredients dissolved in a co-solvent together with the lipophilic components [43]. Ointments are harder to spread or remove as compared to creams and lotions, but they are usually expected to play a barrier role as well as enhance the hydration of the skin [48]. They can demonstrate an occlusive action, effectively restricting the permeation of water and heat. The occlusive property also enhances the penetration and efficacy of the active drug, particularly in areas of thickened skin [6].

3.4. Gels

Gels are semisolid, transparent preparations. Gels are formed by a three-dimensional network created by macromolecules of gelling agents (e.g., hydroxyethylcellulose, carbomers, or carboxymethylcellulose), between which the liquid/solvent is distributed [43]. Based on the character of the solvent, gels can be classified as organogels (apolar phase) or hydrogels (polar phase). Organogels are characterized by their oily nature, whereas hydrogels possess a lighter sensory profile, making them easy to apply, non-greasy, and non-occlusive. Hydrogels are particularly suitable for application on hairy areas or in the treatment of skin conditions such as acne, AD, or seborrhea [43]. Gels may contain some alcohol content, providing refreshing feelings or a colling sensation when applying the product to the skin. The viscosity of gels is low, causing them to liquefy upon contact with the skin and possibly leave a film-like effect on the applied area. Gels are suitable for oily skin or areas with hair. However, due to their lighter characteristics, gels are easily removed with sweat or friction. Gels containing alcohol in their formulation may also cause a stinging sensation on damaged skin [6].

3.5. Pastes

Pastes are also semi-solid preparations. Pastes are characterized by a stiff consistency, achieved through a high concentration of dispersed solid ingredients. They are intended for applications on the skin, oral cavity, or mucous membranes. Due to their persistence on the skin, they have occlusive and protective actions. Pastes and ointments provide skin protection and can be used to absorb secretions [41].

3.6. Foam

Foam is considered a pharmaceutical formulation, typically comprising a substantial volume of gas dispersed within a liquid medium containing one or more APIs. This formulation is generated by the action of a propellant and may also include additional excipients in aqueous phases and/or oily phases [49]. Foams are particularly user-friendly, especially for sensitive skin, as their spreadability requires minimal force for product application [49].

3.7. Spray

Sprays are solution aerosols. They are composed of a solution combined with a propellant gas, which is often a mixture of nonpolar hydrocarbons. The solvents in these sprays may include ethanol, acetone, glycol ethers, and polyglycols. Sprays offer the advantage of effectively covering large areas of affected skin and can also provide a cooling sensation upon utilization. Sprays have a high safety profile because of their low product contamination [51]. However, sprays may cause burning or stinging sensations [6].

3.8. Shampoo/Soap

Soaps and shampoos are topical preparations available in solid or liquid forms. They are intended for application to the skin or scalp, followed by rinsing with water. These products can be classified according to emulsions or surfactant-based compounds that, when applied with water and friction, generate foams. Due to their characteristics, soaps

and shampoos have great ease in reaching a larger area of the body, which is helpful in treating skin conditions like AD [41].

4. Cosmetics as Adjuvants

In recent decades, the cosmetic industry has experienced substantial scientific and technical advancements, particularly in understanding skin physiology and the development of research techniques. These progressions have facilitated the safe utilization of novel APIs and carriers grounded in well-understood mechanisms of action [52,53]. Cosmetics have usually been formulated as products such as powders, lotions, and creams, designed to enhance personal appearance through direct skin application. However, recent scientific and technological progress has transformed comprehension of normal skin physiology and the ways in which cosmetics can alter its appearance through both physical modifications and biological activities [54].

Dermo-cosmetics has emerged as a subspecialty within dermatology, utilizing cosmetic products to treat various skin conditions. They are commonly employed to enhance photoprotection, treat dry or aging skin, and manage inflammatory skin conditions such as acne, rosacea, AD, psoriasis, and seborrheic dermatitis. Additionally, demo-cosmetics contribute to improving the quality of life of patients [55]. The products have proven to be excellent adjuncts in the treatment of AD, as they do not contain corticosteroids but offer formulations rich in moisturizing and emollient agents that aid in the recovery and strengthening of the skin barrier [56]. Furthermore, dermocosmetics has demonstrated the ability to decrease the side effects of pharmacological treatments, offer high levels of patient satisfaction, and increase adherence to treatment regimens. Collectively, reported evidence supports the incorporation of dermocosmetics into clinical practice [50].

5. Cosmetic Formulations

The primary objective in the development of cosmetic formulations across various galenic forms is to ensure the bioavailability of APIs while maintaining physicochemical and microbiological stability and safety and also providing a comfortable skin sensation under in-use conditions. The rationale behind developing an appropriate vehicle, aimed at achieving biocompatibility with the skin and the bioavailability of APIs, is crucial to obtaining an optimal balance between the ingredients of formulations and the skin [54].

The research of Külkamp-Guerreiro et al. [57] showed that consumers preferred free lipoic acid formulations, as this API brought the desired spreadability and residual oiliness. Additionally, the higher viscosity of the product conveyed a sensation of greater hydration for the applied skin area [57]. In psoriasis treatment, poor cosmetic properties have been identified as one of the significant reasons for non-adherence and incorrect application [45]. The sensory aspects of a product, thus, play a central role in users' acceptance and compliance. Accordingly, the sensory attributes as well as the safety and efficacy of the product should be taken into account in cosmetic formulation development.

6. Moisturizers

Healthy skin can improve quality of life and significantly contribute to social interactions and psychological well-being [6]. Skin irritation is the most frequent adverse effect, which can be perceived with or without signs and symptoms of skin inflammation [58].

Moisturizing power is considered one of the most important benefits of a skin product, and this hydration advantage could be divided into four actions: repairing the skin barrier, increasing the water content in the skin, reducing transepidermal water loss (TEWL), and maintaining the skin hydrated [59]. Moisturizers are essential components in any topical formulation for AD treatment, as they restore the ability of intercellular lipid bilayers to absorb, retain, and redistribute water [60]. Moisturizing agents can also penetrate the skin and contribute to the reorganization of skin layer structure. The work of Danby et al. [61] showed the positive hydration effect of emollient creams on the treatment of eczema or AD skin disease via both subjective and objective measurements.

However, even moisturizers, with their benefits, may be linked to cases of allergy, depending largely on the characteristics of the formulations as well as the immune response of each individual. Some possible adverse effects of moisturizers regarding the ingredients present in the formulation include skin irritation reactions (urea, acids, propylene glycol, solvents), contact dermatitis (lanolin, propylene glycol, methylchloroisothiazolinone (and) methylisothiazolinone, some preservatives, fragrances, sunscreens), occlusion folliculitis (lanolin, petrolatum, mineral oil), photosensitivity (fragrances, sunscreens, preservatives, acids), acne (occlusive ingredients), contact urticaria (sorbic acid, fragrances, balsam of Peru), poisoning (salicylic acid), among some examples [58,62,63].

Moisturizers, which are pivotal in topical formulations for AD treatment, can be categorized into primary and secondary types. Primary moisturizers are further divided into two groups: hydrophilic moisturizers (humectants) and lipophilic moisturizers (emollients and occlusives) (as shown in Figure 1) [6,64].

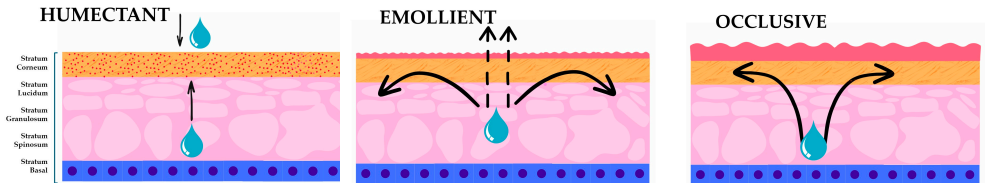


Figure 1. The mechanism of action of moisturizers on the skin [30–33].

Humectants are substances that mimic the natural moisturizing factor (NMF) of the skin [6], enhancing epidermal barrier function and hydration. They may also possess additional properties, similar to those of emollients. Common humectants used in topical formulations include glycerin, acid lactic, propylene glycol, urea, butylene glycol, panthenol, hyaluronic acid, sorbitol, glycolic acid, and sodium pyrrolidone carboxylic acid [6,64].

Emollients are agents that soothe, soften, and increase skin hydration levels. They are commonly incorporated into lotions, creams, ointments, or gels and function by filling the spaces between corneocytes, thereby protecting the skin from irritations, facilitating smooth application, or providing lubrication. Emollients enhance the overall appearance and texture of the skin and are frequently used in conjunction with emulsifiers [65]. Commonly used emollient ingredients in formulations include cholesterol, linoleic acid, squalene, oleic acid, stearic acid, fatty alcohols, and cocoa butter [6,66].

Occlusives emulate the sebum and natural lipids present in the skin. They form a hydrophobic barrier film on the skin's surface, thereby reducing TEWL and preventing water evaporation from the stratum corneum. Commonly used occlusive ingredients include liquid paraffin, lanolin, and white petrolatum, which provide hydration through their occlusive effects [6,64]. However, many occlusives are characterized by a greasy texture, odor, and potential allergenicity [59]. Kovács et al. [66] proposed developing a cream that offers smoothness and hydration benefits without using these traditional occlusive agents. Instead, they utilized sunflower oil and cocoa butter, resulting in a product with significant hydration potential without the occlusive effect of conventional ingredients [66].

7. Effects of Formulation Excipients

The development of topical vehicle formulations necessitates extensive knowledge and a tailored approach based on the physicochemical properties of the APIs, ensuring functionality in the target skin area [6]. A key consideration for formulators is to pay attention to the compatibility and stability of excipients and APIs, both for the product's commercial viability and for maintaining its safety and therapeutic efficacy [36]. "Excipients" are common non-active ingredients used in the formulation of topical vehicles, such as emulsifiers, thickeners, chelating agents, preservatives, pH adjusters, and fragrances. These excipients typically make up more than 90% of a topical product. Formulators

leverage the functionality of excipients to achieve specific performance attributes, for instance, improving solubility for API incorporation, controlling drug release and permeation, enhancing the product's aesthetic appeal to increase patient adherence, improving skin deposition, stabilizing active ingredients and vehicles, and preventing microbial growth and contamination [6,31,32].

7.1. Solvents

Solvents play multiple roles, including enhancing the solubility of APIs and facilitating their absorption through the skin. Solvents are also incorporated to dissolve other excipients, such as colorants and preservatives. Water is the most essential and commonly used solvent in cosmetic product formulations, requiring purity and freedom from contaminants and microbes [64]. Depending on the desired final formulation, other solvents may also be employed, such as propylene glycol, mineral oil, or hexylene glycol. Propylene glycol, in particular, is often used in formulations as a co-solvent to enhance drug permeation through the skin, acting as a skin penetration enhancer [32,34].

7.2. Consistency Agents

Hardening or consistency agents are excipients that form structure in topical semisolid formulations, used with the aim of imparting greater viscosity and stability to the formulations. Examples of these ingredients include beeswax, carnauba wax, white petrolatum, liquid paraffin, and lanolin. Topical formulations containing a high concentration of these consistency agents tend to form a protective occlusive barrier on the skin. This barrier shields the skin from harmful substances and aids in maintaining skin hydration by preventing TEWL [6,34].

7.3. Thickeners/Gelling Agents

Thickeners are critical excipients in topical vehicles, determining their final viscosity, which is directly related to skin retention and penetration of the APIs. Thickeners can be classified into four groups based on their origin:

1. Lipid thickeners (cetyl alcohol, cetearyl alcohol, stearic acid, and carnauba wax) are incorporated into the oily phase of the formulation due to their lipidic nature.
2. Natural thickeners (hydroxyethyl cellulose, carboxymethyl cellulose, guar gum, xanthan gum, gelatin, and sodium alginate) are polymers that absorb water thereby increasing the viscosity of the vehicle.
3. Mineral thickeners (silica, aluminum magnesium silicate, and bentonite) are of natural origin, absorbing water, and oils to increase the viscosity of the formulation.
4. Synthetic thickeners (carbomers, cetyl palmitate, and ammonium acryloyldimethyltaurate). Carbomers are one of the most commonly used thickeners due to their ability to form a transparent gel [6,34,61].

7.4. Silicones

Silicones are ingredients that can act as non-greasy occlusives, aiding in moisture retention, lubricating, and forming an occlusive film on the skin [61]. They function as emollients, providing a pleasant sensation on the skin and creating a desired smooth skin surface. Among various types of silicones, the most commonly used in topical formulations are dimethicone and cyclomethicone [6]. Hand creams, which are oil-in-water emulsions, typically contain between 15% and 40% oils, 5% and 15% humectants, and 45% and 80% water. By adding a specific silicone, due to its hydrophobic action, it is possible to achieve a water-resistant hand cream (through 4 to 6 washes). Most hand creams contain petrolatum, glycerin, waxes, or dimethicone [65]. Some silicones have occlusive characteristics, increasing the potential for allergenicity and imparting a greasy consistency [58].

7.5. Humectants

Humectants are crucial in formulations as they are substances that attract water, acting like sponges and keeping water in the skin. The ingredient content in the formulation must be sufficient to achieve the desired effect, because in lower dosages, it will be ineffective in hydration [65]. One of the most effective ingredients in this category is glycerol. As a humectant commonly used in topical moisturizers, glycerol has been shown to be able to accelerate skin barrier recovery. In the therapy of AD, glycerol is often used at doses varying from 20% to 40%. This is due to its beneficial benefits for the skin, such as hydrating the outermost layer of the skin and restoring the protective barrier. Youssef et al. [67] showed that concentrated glycerol, at a concentration of 85%, may serve as a viable option for patients in need of phototherapy since it effectively reduces staphylococcal presence on the skin and is also more cost-effective compared to the Narrow Band Ultraviolet B (NB-UVB) treatment [67]. In another research work, Danby et al. [61] demonstrated the superior efficacy of glycerol-based moisturizers compared to those lacking a humectant in restoring skin hydration and enhancing filaggrin expression by keratinocytes.

7.6. Emulsifiers/Solubilisers

Emulsifiers are directly related to the stability of topical vehicles, maintaining a uniform product throughout their period of use. Emulsifiers can be polar (hydrophilic) or nonpolar (lipophilic), resulting in greater or lesser affinity with water or oil. Their function is to reduce interfacial tension, thereby stabilizing emulsions and enhancing the wetting and solubility of hydrophobic ingredients [6]. Despite bringing structure benefits to producing good emulsions, emulsifiers can cause dermal irritation and corrosiveness and increase the potential for sensitization when applied in high concentrations [34].

7.7. Chelating Agents

Chelating agents such as ethylene diamine tetraacetic acid (EDTA) are used in formulations to improve the stability of a topical vehicle by binding to metal ions. In this way, they reduce undesirable effects in formulations arising from metal-catalyzed degradation. Chelating agents may also exhibit positive synergy with the effects of preservatives [6]. Their application is extensive, spanning the food and pharmaceutical industries, and they play an extremely important role, such as in countering heavy metal poisoning and reducing cholesterol levels in the blood. According to a comprehensive study conducted by experts from the Cosmetic Ingredient Review (CIR) to extensively examine the safety of chelating agents, various EDTA derivatives have been concluded to be safe for use in cosmetic formulations [68].

7.8. Acidifying, Alkalising, or Buffering Agent

The final pH of a product is crucial to optimizing its characteristics, especially in adapting to the skin's pH. Buffers are often employed to maintain the pH and other vital characteristics of a topical vehicle throughout their shelf life [6]. The pH regulators act to maintain a suitable pH for the delivery of APIs, with the most commonly used being citric acid, lactic acid, phosphoric acid, and sodium hydroxide. The pH of the vehicle is important for maintaining the stability and efficacy of APIs, thereby preventing their degradation. Values of pH can directly affect the effectiveness of the preservatives as well, compromising their preservative effect as well as impacting the viscosity of the product [34]. Nevertheless, products with high buffering capacity require careful consideration, as they have the potential to alter the skin surface, resulting in both positive and negative effects [32].

7.9. Antioxidants

Many topical formulations are susceptible to oxidative degradation. An antioxidant is, therefore, usually used as the important composition to protect the prepared formulation. In oily products, antioxidants prevent oils from becoming rancid. The most commonly used

antioxidants in topical formulations include butylated hydroxyanisole (BHA), butylated hydroxytoluene (BHT), ascorbyl palmitate, and sodium ascorbate [6].

The concept of antioxidants is pertinent in the pursuit of benefits for topical applications. Reactive oxygen species (ROS) can be produced in the skin upon exposure to agents such as stress, UV radiation, environmental pollutants, and inflammation. These ROS cause damage to DNA, RNA, proteins, and lipid bilayers, resulting in skin aging and photocarcinogenesis. Thus, topical antioxidants have been utilized as a means of combating these damages. Chandan et al. [69] demonstrated the active role in the skin's defense mechanism of antioxidant enzymes (specifically superoxide dismutase (SOD) and catalase) in preventing oxidative damage caused by ROS. This could be a highly desired effect for products targeting skin conditions with inadequate oxidative repair, such as AD, psoriasis, and acne [69]. Zhang et al. [70] examined the antioxidant effects of natural extracts containing curly kale, apple, and green tea, which are rich in antioxidants. Their study illustrated that these formulations possessing high antioxidant capacity could exhibit anti-inflammatory effects in patients with mild to moderate AD. The formulations were also found to be able to reduce itching, decrease local SCORAD scores, and improve both barrier function and hydration of skin lesions [70].

7.10. Preservatives

Inclusion of preservatives in topical formulations, particularly those with high water content, is recommended to prevent contamination and microbial growth. In anhydrous formulations, such as ointments, the use of preservatives is less frequent. A preservative should exhibit efficacy against a broad spectrum of microorganisms. Several factors must be considered when selecting a preservative, including the formulation type, toxicity, potential for irritation, concentration within the formulation, and the presence of other preservatives in the ingredients. Some examples of widely used preservatives include alcohols (benzyl alcohol, ethanol, and phenoxyethanol), phenols (chlorocresol), hydroxybenzoates (all salts), and quaternary ammonium compounds (benzalkonium chloride and cetrimide) [6].

Due to their widespread use and significant risk of sensitization, preservatives remain a leading cause of contact allergies. Even the new generations of preservatives necessitate further studies before market introduction. Future preservatives aim to offer broad-spectrum antimicrobial activity while maintaining a high safety profile with respect to sensitization [71]. Preservatives containing chloromethylisothiazolinone (MCI) and methylisothiazolinone (MI) were widely used in cosmetic products due to their antimicrobial efficacy. However, since 1985, its sensitizing effect in cosmetics has been documented. Clinical symptoms primarily affect the hands and faces of patients using products such as gels, liquid soaps, and shampoos. This sensitization is intrinsically linked to multiple contact hypersensitivities, predominantly involving fragrances [72].

7.11. Fragrance

Fragrances are important for the attractiveness of cosmetic products. Their composition is complex, with a large number of ingredients, either from natural or synthetic origins. Fragrance allergens are the main cause of contact allergies, especially in children. A higher number of allergenic fragrances were found in facial products, with facial eczema being the most common scenario [73]. Besides, Travassos et al. [74] conducted a study with 11 different categories of cosmetic products containing non-perfumed allergens for the skin, hair, and body. Formaldehyde-based preservatives were found to be the major culprits for allergies, and the sunscreen ingredient octocrylene was also identified as an allergen [74].

Table 2 summarizes some of the usual inactive ingredients or excipients used in topical formulations.

Table 2. Excipients used in topical formulations.

Excipient	Role	Example	Other Function
Solvents [32,34,64]	vehicle, dissolve excipients	water, propylene glycol, mineral oil, and hexylene glycol	water, the most essential and commonly
Consistency agents [6,34]	hardening or consistency	beeswax, carnauba wax, white petrolatum, liquid paraffin, and lanolin	protective occlusive barrier
Thickeners/Gelling agents [6,32,34]	viscosity control	cetyl alcohol, cetearyl alcohol, carnauba wax, stearic acid, gelatin, hydroxyethyl cellulose, xanthan gum, carboxymethyl cellulose, guar gum, sodium alginate, bentonite, aluminum magnesium silicate, ammonium acryloyldimethyltaurate, silica, acetyl palmitate, carbomers	viscosity is directly related to skin retention and the penetration of actives
Silicones [6,32]	smooth skin surface	dimethicone, cyclomethicone	ingredients that can act as non-greasy occlusives
Humectants [65,67]	attract water	glycerin	accelerate skin barrier recovery
Emulsifiers/Solubilisers [6,34]	stability control	glycerol monostearate, cetostearyl alcohol, cetyl palmitate, sorbitan monostearate, polysorbate 20, polysorbate 60, polysorbate 80, propylene glycol monostearate, sorbitan monooleate, poloxamer, emulsifying wax, sodium lauryl sulfate, and diethylene glycol monoethyl ether	higher percentage can cause dermal irritation, corrosiveness, and an increased potential for sensitization
Chelating agents [6]	improve the stability of a topical vehicle	EDTA	may exhibit positive synergy with the effects of preservatives
Acidifying/Alkalising/ Buffering agent [6,32,34]	buffering, pH agent	citric acid, phosphoric acid, lactic acid, and sodium hydroxide	correct skin pH; help to delivery of actives; and maintaining the stability and efficacy of an active ingredient
Antioxidants [6]	composition protection	BHA, BHT, ascorbyl palmitate, and sodium ascorbate	prevent oil rancidity
Preservatives [6]	prevent contamination	benzyl alcohol, ethanol, phenoxyethanol, quaternary ammonium compounds (benzalkonium chloride, cetrimide), hydroxybenzoates (all salts), phenols (chlorocresol)	extend shelf life
Fragrance [6,73]	perfume the product	natural or synthetic origin	attractiveness of cosmetic products

8. Conclusions

A consensus exists that AD is recognized as a chronic condition, attributed to various factors, including a genetic component, requiring ongoing management throughout the patient's life. Therapeutic interventions may include oral medications, such as corticosteroids and immunosuppressants, alongside topical corticosteroids applied directly to the

skin. Additionally, the use of moisturizers as an adjunct therapy is recommended for deep hydration.

Several scientific studies have emphasized the importance of cosmetics as adjuncts in AD treatment, with their utilization and recognition of benefits gaining increasing strength. In addition to the hydration provided by cosmetic products, the final sensory experience delivered after application stands out as a crucial factor for patient adherence to AD treatment.

A cosmetic formulation for AD needs to be comprehensively balanced, and the significant contribution of a cosmetic lies in its ability to deeply hydrate compromised, dry, and fragile skin. This review places a greater emphasis on exploring hydration alternatives (emollient, humectant, and occlusive).

Essential concepts for the effective development of safe and modern cosmetics were also addressed in this review. This material aims to contribute to the dissemination of knowledge on aspects and concepts related to product development, providing strategic information for formulators to create products that enhance self-esteem, in addition to improving skin appearance and providing a pleasant sensation.

Despite extensive research highlighting the importance and benefits of cosmetic vehicles, testing standards for cosmetic products must evolve accordingly. It is crucial that assays evaluating the efficacy and safety of cosmetics and dermo-cosmetics adhere to rigorous, scientifically sound methodologies in line with the latest approved guidelines.

There is a lack of scientific studies addressing the quality and control of the water used in the development of topical products. Considering that water often constitutes the largest percentage in formulations, it is crucial for new studies to focus on this significant ingredient applied in formulations.

Several vehicles can alter the potency, sensory properties, safety, and efficacy of a formulation for AD. This scientific article addressed key points for the development of a cosmetic product for AD, thus contributing to assist the formulator in developing a safe and effective formulation.

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