



Review Article

Understanding Your Creams: Principles of Dermatological Formulation

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Abstract

Traditionally in Medical and Dermatological training, the focus has been on the understanding, diagnosis and management of skin diseases, including treatment using topical formulations. With the exception of learning about the pharmacologically active ingredient, there is a neglect and gap in understanding the other ingredients that comprise a topical formulation, which is a prime tool in our therapeutic armamentarium. Such an understanding is essential to allow for skilful deployment of treatments, management of problems these applications can secondarily cause, and the formulation of more suitable agents for individual or commercial use. This article examines the composition of a topical product, including its active ingredient (s), common topical vehicles used for drug delivery, and additives, paying particular attention to how these ingredients interact with the skin for absorption and which of them are more likely to cause contact dermatitis.

Keywords: Topical, Ointment, Gel, Skin; Transcutaneous; Transdermal

Introduction

Prescribing effective topical therapies is fundamental in the treatment of dermatological conditions. Delivering drug molecules to and through the skin requires a complex interplay between the different components of the topical formulation: the active drug, the carrier system or 'vehicle', the excipients, and an individual's skin type, location, and skin condition [1].

Following application of a topical agent onto the skin, volatile components of the formulation evaporate, and the ingredients within the formulation are released (*liberated*) to become potentially bioavailable [2]. The final bioavailable portion to the skin (the acceptor) is still dependent on various factors: the severity of the condition, and the acceptor's properties, which may differ inter- and intra-individually, and change over the course of the healing process [2].

The *liberation rate* depends on the composition of the vehicle, the physicochemical properties of the (active) ingredient(s), as well as the properties of the skin (acceptor) [2]. After liberation,

the ingredients undergo penetration across the various skin layers [2]. The first and main barrier which the chemicals need to penetrate is the stratum corneum (SC) [2]. Penetration through the SC after application is an important time-sensitive parameter as the preparation might be wiped away from the skin surface by clothing or otherwise. The chemicals then diffuse through the skin layers via the intracellular and/or intercellular routes [2]. The most important route is intercellular, which in turn comprises hydrophilic and lipophilic pathways. The hydrophilic pathway utilizes the hydrophilic head groups of ceramides and interacting water molecules (in a membrane-like molecular arrangement) for diffusion. In the lipophilic pathway, flexible lipophilic side chains of ceramides serve as matrix for penetration [2].

The ingredients are then distributed to the different skin layers, taking into consideration various factors described in Fick's laws of diffusion: concentration differences, diffusion surface, diffusion distance, and diffusion properties of individual compartments (diffusion coefficient) [2].

Composition of a Topical Product

A topical product typically consists of an active ingredient, the topical carrier system (vehicle) and its components, as well as any additives, including preservatives, pH buffers, penetration enhancers, antioxidants and chelating agents and fragrances.

Active Ingredient

The active ingredient or "agent" is the main ingredient within topical product. This is usually the medicinal component with a therapeutic effect. Common classes of active ingredients include anti-inflammatory, antimicrobial, anti-proliferative, and immunomodulatory agents. Physical and chemical properties of the active ingredient must be taken into account to optimize absorption. Firstly, the active ingredient needs to be of a molecular weight of less than 500 Daltons in order to penetrate the intact SC. Besides molecular size, other properties of the molecule also play a role in absorption, such as the lipophilicity of the molecules or log P which should ideally be around 2-3 and with measurable water solubility [3].

Vehicle

The topical carrier system, or vehicle, is defined as the substance that carries the chosen active drug across the stratum corneum to penetrate deeper into the skin at appropriate concentrations sufficient to provide a therapeutic effect [1].

The intact SC is considered to be the major barrier for drug penetration, generally considered to be only permeable to compounds and molecules with a molecular weight below 500 Daltons [3]. The chosen vehicle should be able to maintain stability of the active ingredient, to allow swift penetration through

the SC and diffusion through the various skin layers, and release the active drug in a timely manner. It should also be able to sustain the active drug at the target site for a sufficient duration to exert a therapeutic effect, while limiting systemic absorption [1].

Common forms of the vehicles include ointment, cream, gel and lotion. The choice of vehicle form should take into account its ability to soothe, spread easily and be aesthetically pleasant. Importantly, it should also take into account the user's preference, as this closely affects compliance. For example, an oil-based formulation such as ointment may leave behind sticky residue, as compared to a more water-based formulation such as a cream or gel, which may be a reason for preference for a cream over ointment as a choice of vehicle. Additionally, the vehicle should not cause discomfort, worsening of the skin condition or allergies after application [1]. Examples of vehicle formulations from the German Pharmacopoeia that are usually non-allergenic include Hydrophobic basic gel DAC, Cooling cream DAB, Macrogol ointment DAC, Soft zinc paste DAB, Zinc oxide shake lotion DAC, unpreserved Hydroxyethyl cellulose gel DAB [2].

Additives

Certain additives such as antimicrobial preservatives, penetration enhancers, antioxidants and chelating agents, buffers and fragrances can be included in the formulation. Depending on the purpose of the topical formulation, one or more of the following additives may be utilised.

Antimicrobial Preservatives

Topical formulations often contain several ingredients, which readily support the growth of a variety of microorganisms. One such commonly used ingredient is water. Hence, topical formulations usually incorporate antimicrobial preservatives to reduce microbial contamination of the product. Commonly used preservatives include alkyl hydroxybenzoates (parabens) and benzoic acid.

Preservatives should ideally have a wide spectrum of antimicrobial activity with a high preservative capacity. More importantly, it should be non-toxic, and have a low irritant and allergy-inducing potential. To ensure stability of the topical formulation, preservatives should be compatible with other ingredients and the packaging, which it is contained. They should also remain stable and effective over a wide pH and temperature range, and are preferably colorless and odorless [4].

Penetration Enhancers

The skin is a remarkable barrier designed to keep out foreign substances. While this is helpful in preventing infections, it poses great hindrance to the penetration of topical formulations through this barrier quickly enough before it is unintentionally wiped

away. One approach that formulators use to overcome this barrier is to incorporate penetration enhancers, also known as sorption promoters or accelerants, which can interact with skin constituents to promote drug flux [5]. Ideally, penetration enhancers should work rapidly with a reproducible and predictable activity and duration of effect. It should also be non-toxic, non-irritating, and non-allergenic, be cosmetically acceptable, and be able to work with a diverse selection of topical preparations. It should not have any pharmacological effect on the body, and its effect on barrier properties of the skin should be reversed once removed from the skin. Penetration enhancers should work uni-directionally, that is, to only allow the therapeutic agent to penetrate while not promoting the loss of endogenous material from the body [5].

Water is considered a penetration enhancer as tissue hydration appears to increase transdermal delivery of topical agents [5]. *Ethanol* is another commonly used enhancer that permeates the stratum corneum, increasing lipid chains movements within the phospholipid bilayers, facilitating improvement of drug partitioning into the membrane. It can concurrently act as a solvent to increase solubility of the active ingredient in the vehicle. In addition, ethanol evaporates quickly and leaves behind the drug in a supersaturated concentration on the skin, increasing the driving force for permeation [5]. *Fatty alcohols (or alkanols) and propylene glycol* are also examples of penetration enhancers which are usually added together as co-solvents. Propylene glycol is widely used as a penetration enhancer and can permeate well through the SC [5].

Surface-active agents, or surfactants, are composed of a hydrophilic head and a hydrophobic tail. When a sufficient amount of surfactant is added into these formulations, they aggregate to form spherical structures called micelles. These act to solubilize lipophilic active ingredients, but at the same time, they can also solubilize lipids within the stratum corneum and cause irritant reactions. Surfactants are grouped into 4 major groups: anionic, cationic, amphoteric (exhibiting both anionic and cationic dissociations) and non-ionic [6]. A common example of anionic, cationic, and non-ionic surfactants that are used within topical formulations are sodium lauryl sulphate (SLS), cetyltrimethyl ammonium bromide, and polysorbate, respectively [5].

Novel Penetration Enhancers-Drug Encapsulation and Nanoparticles

There have been advances in technology involving penetration enhancers, where novel drug delivery systems have been developed to improve drug delivery. One example is the use of drug encapsulation. As its name suggests, these delivery systems comprise a variety of therapeutic agents that are encapsulated within a biopolymer, providing a suitable environment for these drugs to be in, hence improving the solubility and stability

of these molecules while reducing biodegradation [7,8]. This curbs some of the pharmacokinetic limitations that these drugs might potentially have, such as poor bioavailability, creating an opportunity for such drugs to be reincluded as potential therapeutic agents in the treatment of skin diseases [7]. Some successful examples where drug encapsulation have been used in topical formulations include liposomes, solid lipid nanoparticles (SLN), and biodegradable polyester nano-particles such as Poly-Lactic Acid (PLA), Poly-Lactide-Co-Glycolide (PLGA) and Poly-ε-Caprolactone (PCL) [7,8]. These nanocarriers allow a sustained and controlled release of drug particles, allowing maximal exposure of the site of application to the drug while maintaining an appropriate therapeutic concentration at the site with minimal systemic absorption. Examples of dermatological drugs that are delivered across the skin using nanoparticles in studies include minoxidil, triamcinolone acetonide acetate and cyclosporin A [7].

Antioxidants and Chelating Agents

The function of antioxidants is to prevent oxidative degradation of compounds. Many organic compounds are subject to auto-oxidation upon exposure to air. One example is unsaturated oils, such as vegetable oils, that can become rancid and give off an unpleasant odor. Mineral oils, on the other hand, are less sensitive to oxidation [9,10]. Examples of antioxidants include Butylated Hydroxytoluene (BHT), Butylated Hydroxyanisole (BHA), L-tocopherol and alkyl gallates [11]. Combinations of two or more antioxidants have been shown to produce synergistic effects. For example, BHT, BHA and alkyl gallates are much more effective in the presence of citric, tartaric or phosphoric acids [12].

Chelating agents are included if traces of metallic ions are likely to catalyse oxidative degradation of the active ingredients. Examples are citric acid, maleic acid, phosphoric acid and ethylenediamine-tetra-acetic acid (EDTA). EDTA plays a dual role in many pharmaceutical products – in addition to providing a chelating effect, it possesses a small amount of antimicrobial activity which can potentiate the action of many established preservatives [4].

Buffers

Buffers are solutions of compounds that can resist pH changes upon dilution or addition of small quantities of acid or base. The choice of buffer is dependent on the pH and buffer capacity required for the purpose of the formulation. Buffer capacity measures the magnitude of resistance of a buffer to pH changes through the addition or removal of H⁺ or OH⁻ ions. Buffers in pharmaceutical formulations should have pH and buffer capacity that maximize tissue compatibility, and the solubility and stability of buffer constituents and drug [13]. The acetate buffer system, containing acetic and acetate salts are widely used in cosmetic ingredients and skin-conditioning agents [14].

The pharmacopoeias contain specific instructions on the ingredients and their required concentrations to be added into a formulation in order to produce various buffer systems of specific pH ranges. For example, to create an acetate buffer solution of pH 4.4, the European pharmacopoeia specifies 136g of sodium acetate and 77g of ammonium acetate to be dissolved in water and diluted to 1000ml, then mixed with 250ml of glacial acetic acid [15].

Fragrances

There are multiple roles for the addition of fragrances into topical formulations. Some fragrances have actual functionality, such as certain essential oils, like thyme oil, which have antimicrobial properties. Fragrances can also influence the consumer’s purchase decisions, for example by adding a “medicinal” smell in anti-dandruff shampoo, or to mask inherent unpleasant odors from the raw materials used in certain products [16].

Balsam of Peru is a fragrance of plant origin that is frequently used in cosmetics, pharmaceuticals, and flavorings. Besides adding an aromatic component, it also has antibacterial, antifungal, and anti-scabetic activities [17].

Colorants

Colorants are inactive substances that may be deployed in a topical formulation for non-therapeutic purposes, such as to identify and distinguish between medications, and to tell apart different strengths of the same medication. They can also be used to enhance the aesthetic appearance of a preparation [18].

As concerns about the toxicity of artificial colorants continue worldwide, plant-derived colorants are increasingly being used in place of synthetic dyes. An example is turmeric from the roots of *Curcuma longa*, which contains curcuminoids and is yellow or orange in color. β -Carotene is another example, which is orange-yellow in color. Other plant-based colorants used in place of synthetic dyes include anthocyanins and tomato extract, which produce a range of red colors. However, the major problem of using plant extracts for coloring is that they tend to be unstable in varying pH conditions and are prone to degradation [4].

A topical formulation contains a large variety of different ingredients, each with their own purposes. The ingredients that have been stated above, their examples as well as their ideal properties have been summarized in Table 1.

| Ingredient | Function | Other considerations for selection |
|---|--|---|
| <p>1. Active ingredient E.g. Inflammatory, antimicrobial, antiproliferative, and immunomodulatory agents</p> | Main ingredient medicinal component with a therapeutic effect. | <ul style="list-style-type: none"> • Molecular weight of less than 500 Daltons • Log P should ideally be around 2-3 • Measurable water solubility |
| <p>2. Vehicle E.g. Ointment, cream, gel and lotion</p> | Topical carrier system. Carries the chosen active drug across the stratum corneum. | <ul style="list-style-type: none"> • Soothing • Spread easily • Aesthetically pleasant • Indicate user’s preference • Should not cause discomfort, worsening of the skin condition or allergies after application |
| <p>3. Antimicrobial preservatives E.g. Alkyl hydroxybenzoates (parabens) and benzoic acid</p> | Reduce microbial contamination of the product. | <ul style="list-style-type: none"> • Wide spectrum of antimicrobial activity with a high preservative capacity • Non-toxic • Low irritant and allergy-inducing • Compatible with other ingredients and the packaging • Stable and effective over a wide pH and temperature range • Colorless and odorless |

| | | |
|--|--|--|
| <p>4. Penetration enhancers E.g. Water, ethanol fatty alcohols (or alkanols), propylene glycol, surfactants, liposomes, nanoparticles</p> | <p>Overcome the skin barrier. Can interact with skin constituents to promote drug flux.</p> | <ul style="list-style-type: none"> • Work rapidly • Reproducible and predictable activity and duration of effect • Non-toxic, non-irritating, non-allergenic • Cosmetically acceptable • Able to work with a diverse selection of topical preparations • No pharmacological effect on the body • Effect on barrier properties of the skin should be reversed once removed from the skin • Work uni-directionally |
| <p>5. Antioxidants E.g. Butylated hydroxytoluene (BHT), Butylated Hydroxyanisole (BHA), L-tocopherol and alkyl gallates</p> | <p>Prevent oxidative degradation of compounds.</p> | <ul style="list-style-type: none"> • Combinations of two or more antioxidants to produce synergistic effects |
| <p>6. Chelating agents E.g. Citric acid, maleic acid, phosphoric acid and Ethylene-Diamine-Tetra-Acetic Acid (EDTA)</p> | <p>Included if traces of metallic ions are likely to catalyze oxidative degradation of the active ingredients.</p> | <p>Some chelating agents such as EDTA also possess a small amount of antimicrobial activity which can potentiate the action of many established preservatives.</p> |
| <p>7. Buffers E.g. Acetic and acetate salts</p> | <p>Resist pH changes.</p> | <p>pH and buffer capacity that maximize tissue compatibility, solubility and stability</p> |
| <p>8. Fragrances E.g. Essential oils, Balsam of Peru</p> | <p>Multiple roles such as adding a “medicinal” smell or mask inherent unpleasant odors.</p> | <p>May have antimicrobial properties.</p> |
| <p>9. Colorants E.g. Turmeric, β-Carotene, anthocyanins and tomato extract</p> | <p>Enhance the aesthetic appearance. Identify and distinguish between medications.</p> | <p>Plant extracts for coloring pose a major problem in that they tend to be unstable in varying pH conditions and are prone to degradation.</p> |

Table 1: List of ingredients that comprise a topical formulation; their examples, uses and other considerations for selection.

Contact Dermatitis-Inducing Ingredients

The active ingredients within topical formulations are often thought to be the cause of skin irritation or allergy. However, the other ingredients that constitute the topical preparation may instead be the cause or play a contributory role to the skin reaction. The allergy or irritation is exacerbated when the skin is major barrier, the SC, is compromised, allowing antigens to penetrate more easily. These antigens may intrinsically be weak contact allergens or irritants, but their effects are amplified when applied in conjunction with other weak antigens due to polysensitization [2] Ingredients with sensitization rates of <1 % in larger study populations can be regarded as low [2].

Haptens are non-immunogenic low molecular weight molecules. They are not antigens by themselves but after they penetrate the stratum corneum, they conjugate with larger epidermal and dermal proteins to form complexes, which have

antigenic properties capable of causing contact allergies. Common haptens include nickel, formaldehyde and preservatives [19].

Allergenic Preservatives

Preservatives are essential agents within a topical formulation as it helps to prevent spoilage and hence prolong a product’s shelf life. Unfortunately, many of the preservatives have been recognized as important skin sensitizers and the choice of preservatives available for selection have dwindled [4].

An important and well-known class of preservatives is parabens (commonly methylparaben, ethylparaben, propylparaben and butylparaben). Parabens have been widely used in numerous topical formulations, including cosmetics and medicinal products. With a sensitization frequency of less than 1% in larger population testing, parabens are considered safe from causing contact dermatitis, only with the exception of application onto deep

skin lesions, such as venous ulcers, where sensitization rates are known to be higher [2]. For patients with skin defects, including skin barrier defects such as eczema, it is recommended to use topical preparations low in preservatives or to completely avoid preservatives with high incidence rates of contact dermatitis [2].

Other important preservatives that are well-known sensitizers and potent allergens include isothiazolinones (mainly methylchloroisothiazolinone (MCI) and methylisothiazolinone), Methyl dibromo glutaronitrile (MDBGN), formaldehyde and formaldehyde-releasers, and Iodopropynylbutylcarbamate [20].

According to existing toxicology data, given that the parabens methylparaben and ethylparaben (as well as their salts) have a significantly lower allergic potential compared to preservatives such as methylisothiazolinone, methylchloroisothiazolinone, they are considered safe in cosmetic products at concentrations up to 0.4 % and 0.8 %, respectively. Methylparaben and propylparaben are virtually the only parabens that are used in finished medicinal products and extemporaneous preparations [2].

Irritation- and Allergy-Inducing Penetration Enhancers

For surfactants, anionic and cationic surfactants are generally considered more damaging to the skin, while non-ionic surfactants are considered safer. Ionic surfactants can swell the stratum corneum and interact with intercellular keratin. SLS in particular is a surfactant that is frequently used in experimental studies for the induction of irritant contact dermatitis [21].

In situations, which skin barrier defects occur, especially when there are pre-existing conditions such as asteatotic and atopic dermatitis, the penetration enhancers can further act as sensitizers inducing allergic contact dermatitis. Propylene glycol is an example, which can act as both an irritant and a weak sensitizer [22].

Allergenic Fragrances

Fragrance ingredients are usually self-regulated by the fragrance industry involving two main international fragrance organizations - the International Fragrance Association (IFRA) and Research Institute for Fragrance Materials (RIFM). The IFRA standards define safe use levels for the individual fragrance ingredients, restricting or even prohibiting use of fragrances that cause adverse effects, such as skin irritation, skin sensitization or photoeffects [23,24].

Fragrance allergies can occur in 1% of adults with or without history of atopy [25]. Some common allergenic fragrances include fragrance mix, Balsam of Peru, and cinnamic aldehyde [17]. People with history of allergy to Balsam of Peru should be advised to avoid components that are related to Balsam of Peru, such as Benzyl salicylate, Benzyl alcohol and Benzoic acid, as cross

reactions may occur [26]. Additionally, users can also develop sensitivity to the fragrance overtime with incremental sensitization. A fragrance allergy may be diagnosed through patch testing, which usually include the common baseline series of allergens, including Balsam of Peru, Fragrance Mix I, and Fragrance Mix II [25]. It is advisable for the fragrance-allergic patient to avoid products that contain any fragrances or are unlabeled. Difficulties can arise when certain essential oils are used and labeled on the packaging instead of the fragrance ingredients [17]. For example, cinnamon oil contains cinnamic aldehyde and eugenol, which are components of Fragrance Mix used in patch testing [27].

Allergenic Botanical Extracts

Plant extracts and herbal remedies are becoming an increasingly popular choice of ingredient in over-the-counter products. They are primarily added for fragrance and their supposed healing properties [28]. However, they have also increasingly been recognized as potential causes of contact dermatitis [29]. A wide range of plant derivatives are used for the manufacture of medicinal products. These include fresh and dried plant material, acellular products, and a wide range of botanical extracts of varying purity levels [4].

Common sources of botanicals that are used in medicinal products include Aloe, Arnica flowers, Balsam of Peru, Centella asiatica (i.e., Asiatic pennywort), Lavender oils, peppermint and tea tree oil [17,30]. In a prospective study conducted over a 2-year period involving 29 patients, 34 % of patients demonstrated positive patch-test reactions to Balsam of Peru and 79% to Fragrance Mix I. Patients in this study were also tested with other plant extract allergens, and results showed most common reactions to Compositae plants (39%) and tea tree oil (24%) [30].

Safety Precautions to Prevent Onset or Exacerbation of Skin Conditions Due to Use of Topical Formulations

In sensitive skin individuals, safety precautions should be observed before a topical formulation is introduced. When using a topical product for the first time, patients can carry out a Repeated Open Application Test (ROAT) first [31]. In ROAT, the patient is to apply the product onto a patch of healthy hairless skin that is free from dermatitis or frequent sun exposure. Sites that can be used for ROAT include the hairless side of the forearm, the inner bend of the elbow, behind an ear or the side of the neck [31]. The product should be left on or washed off depending on the manufacturer's or prescriber's instructions for use. The application should be repeated twice a day for a week so as to look out for delayed-type allergic contact dermatitis, or sensitization that has occurred due to the build-up of product in the skin over prolonged repeated use [31].

Conclusion

Topical preparations are a key tool in the management of dermatologic skin conditions. Understanding of the constituents within a topical formulation can help prescribers make an informed decision on selecting the most suitable type of formulation for the respective indication. Given the great variety of vehicles and additives (antimicrobial preservatives, penetration enhancers, antioxidants and chelating agents, buffers and fragrances) that can be included in a formulation, prescribers and formulators can consider selecting a particular ingredient to utilize their primary function as well as other intrinsic effects they might have. Knowledge of the problems that these ingredients may secondarily cause can also aid management. It is recommended for patients with sensitive skin to carry out ROAT for newly prescribed topicals to prevent onset or worsening of skin conditions.

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