THERAPEUTIC UPDATE


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Principles and Approaches for Optimizing Therapy With Unique Topical Vehicles

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Topical therapies are a cornerstone of dermatologic practice. Applying treatments topically yields a host of advantages over other routes of administration. With topical treatment, a potentially high concentration of drug can be delivered directly to the area affected with minimal to no systemic adverse effects.[1] However, topical treatment also entails unique challenges. The mechanism of absorption through the skin is complex, and many drugs do not diffuse easily across the skin barrier. Furthermore, the architecture of different parts of the skin varies, presenting barriers to successful outcomes. Lastly, topical application entails an element of subjectivity, allowing efficacy to be impacted heavily by the compliance and understanding of the patient. However, many of the challenges can be addressed by proper selection of a topical vehicle.

Traditional vehicles for topical therapies are not only efficacious in the treatment of a variety of skin disease, but they are specially formulated to allow for ease of use and applicability to specific parts of the body. These traditional topical treatments often come in the form of ointments, creams, and solutions. Newer generations of topical vehicles have included new textures, including gels, foams, as well as other inventive new delivery systems such as nanoparticles and liposomes (Table 1). There has also been new interest in designing vehicles to improve penetration and allow for the delivery of two or more drugs in order to achieve a synergistic effect.

Percutaneous Absorption

One of the essential functions of the skin is that of a barrier to the outside world. It protects other vital organs by keeping foreign substances from entering the body and by keeping required substances such as water and electrolytes from exiting the body. The primary skin barrier is composed of the stratum corneum, a thin layer of columnar cells called corneocytes held together with a number of intercolating lipids.[2] The diffusion capacity of a given area of skin is determined not only by the thickness of the stratum corneum (which varies) but also by the lipid makeup of that area.[3,4]

These two variables present different challenges and opportunities for drug delivery. First, the tight network of corneocytes keeps foreign substances out. It is widely accepted that channels can be created between corneocytes through hydration. Therefore, substances that hydrate the skin will more likely allow for transcutaneous diffusion. Secondly, the lipid matrix presents a strong hydrophobic barrier between corneocytes. As a result, substances that are hydrophobic or nonpolar will move more easily through the stratum corneum. Additionally, detergents or emulsifying agents may be added to vehicles in order to weaken the skin barrier. Drug delivery vehicles exploit all of these principles in order to allow for transcutaneous diffusion.

Traditional Vehicles

Ointments

Ointments represent the least fluid or spreadable of the three traditional topical vehicles. Their thick texture adds the advantage of giving them occlusive properties. These properties can be hydrating, by helping the epidermal barrier to trap water. This hydration is also helpful in creating channels between corneocytes in order to aid in drug delivery. They tend to have

TABLE 1.

Characteristics of Major Drug Delivery Vehicles

Vehicle	Composition	Advantages	Disadvantages
Ointment	Homogenous, semi-solid preparation with a high viscosity	• Occlusive effect for increased hydration • Can be used on thickened skin lesions	• Greasy or messy application • Insoluble in water, thus difficult to wash off
Cream	Emulsion of oil and water in variable proportions	• Occlusive effect for increased hydration • Can be used on thickened skin lesions	• Less hydrating and less occlusive than ointments • May feel oily due to thick consistency
Solution	Clear and homogenous liquid composed of one or more solutes dissolved in an aqueous, non-aqueous or hydroalcoholic solvent	• Simple formulations • Easily spreadable • Ease of application to hair-baring areas • Little impact on cosmesis	• No occlusive, hydrating or emolliating properties • May cause stinging, dryness or irritation (due to alcohol base)
Gel	Semisolid emulsion formulated as a colloidal dispersion in an aqueous or alcohol base	• Stabilizing properties for active ingredients • Cooling effect on application • Quick drying • Ease of use on hair-baring and non-hair baring areas • Little to no impact on cosmesis	• Little to no occlusive effect • Little hydration • Low side effect profile (burning, itching, redness of skin)
Foam	Pressurized liquids with a propellant that produce a liquid or semi-solid product on valve actuation	• Enhanced absorption of drug • Application advantages (minimal residue, quick drying, spreadable) • Ease of application, especially to hair-baring areas • Little impact on cosmesis	• No occlusive effect • Little to no hydration • May result in burning or stinging on abraded skin

a greasy character, which is helpful for moisturization of dry skin.[5] However, this greasy texture often limits patient compliance and leads patients to prefer other vehicles.[6,7]

Creams

Creams are significantly less greasy, less viscous, and more spreadable than ointments. They generally fit into one of two classes: oil-in-water emulsions or water-in-oil emulsions. The choice of vehicle is based on solubility of the drug in question, with oil-in-water emulsions being best suited for water-soluble drugs, and water-in-oil emulsions better suited for lipid-soluble drugs.[5] Creams are also used for their moistening and emollient properties, which make them advantageous for both dry and weepy/exudative skin conditions, especially those with serous exudate. Many patients prefer creams to ointments for their spreadability and lack of greasy texture. However, they are less hydrating due to little or no occlusive effect.

Solutions

Solutions are liquids composed of one or more solutes dissolved in an aqueous, non-aqueous or hydroalcoholic solvent. With a minimum of only two ingredients, solutions are the most easily formulated topical drug preparations. Their liquid state makes them the most spreadable of traditional drug delivery vehicles. This spreadability is especially useful for drug delivery to the scalp and other hair-bearing areas.[5] However, the texture of solutions does not allow for any occlusive effect as well as only marginal hydration.

Next Generation Vehicles

Gels

Gels are semisolids composed of organic macromolecules organized in a lattice. They are formulated as a colloid with a water, alcohol, acetone, propylene glycol or other substance serving as a base.[5] Gels are often preferred by patients due to their ease of use on both hair-bearing and non hair-bearing areas and for their lack of impact on overall cosmesis. They liquefy on contact with the skin and dry quickly, forming a non-occlusive film limiting their utility as an occlusive emolliating vehicle.

The gel vehicle has helped to overcome some of the limitations of traditional topical drug delivery vehicles. Dapsone, a sulfone based drug that possesses both antimicrobial and anti-inflammatory activities, was once used systemically for the treatment of acne. While it was effective against nodulocystic acne when used orally, it had an unfavorable side effect profile (agranulocytosis, hemolysis), making a topical preparation desirable.[8] Dapsone's insolubility in aqueous solvents stood in the way of topical preparations using the traditional vehicles mentioned above.[9] This limitation was overcome using a diethylene glycol monoethyl ester (DGME)-based gel formulation.[10] This gel-based formula has superior solubilizing properties to other vehicles and allows for facilitated penetration while allowing excess drug to remain in the pilosebaceous unit (an intrinsic property of DGME), serving as a reservoir for time-release.[10] Dapsone 5% gel has shown to be effective against acne in clinical trials with little to no systemic toxicity.[11,12]

The stabilizing properties of gels are also desirable in order to deliver two drugs at once, minimizing interactions and providing a synergistic effect. One such synergistic combination, which has been approved for treatment of acne, is adapalene 0.1%/benzoyl peroxide 2.5% gel (trade name Epiduo). The aqueous gel vehicle for this combination drug provides increased drug stability, as well as even dispersion of both active agents, though the mechanism responsible is not described. Pooled data from several randomized control trials show that efficacy of adapalene/benzoyl peroxide drug combination is greater than either of the two alone, and than the effect of both combined.[13] Furthermore, the aqueous gel vehicle also produced a reduction in lesions on its own, through a mechanism that has not been elucidated.[13]

Foams

While current dermatologic products are dominated by semi-solid compositions, such as creams, ointments and gels, innovative foam vehicles are gaining significant interest given their apparent application advantage, increased skin absorption and improved cosmetic appeal. Foams are pressurized liquids containing active agents, propellants, surface-active agents, and solvents that, upon valve-actuation, produce a liquid or semi-solid product with the propellant subsequently evaporating.

A review of the literature finds that topical foam technology demonstrates superiority over traditional drug delivery vehicles. Gottlieb et al evaluated the efficacy and tolerability to clobetasol propionate foam amongst 279 patients, revealing almost complete resolution of patients' plaque-type psoriasis at non-scalp sites compared to placebo: a 68% and 21% reduction, respectively.[14] Foam vehicles may also represent a new way to effectively treat acne vulgaris without the risk percutaneous absorption of retinoids and subsequent systemic toxicity, an undesirable side effect with the potential for teratogenicity. A study by Jarratt et al found significantly higher plasma concentrations of tazarotenic acid and tazarotene (as measured by area under the plasma concentration-time curve and maximum plasma concentration) after application of tazarotene gel compared to foam.[15] Huang et al. presented a series of in vitro studies investigating the mechanisms underlying enhanced skin penetration of foam vehicles. Authors found that foam vehicles had the ability to deliver a greater amount of active drug at an increased rate compared to other vehicles as measured by flux of ketoconazole through a synthetic lipophilic barrier membrane, with an 11-fold increase in total absorption of the drug.[16] Researchers hypothesize that the rapid evaporation of propellants from the skin surface influences and increases the rate of drug transfer from vehicle to skin; as the volatile components evaporate, the drug becomes suspended in a saturated (and ultimately supersaturated) solution, maximizing the vehicle-skin interface.[17] Lastly, the favorable safety profile and clinical efficacy of ketoconazole foam 2% for the treatment of seborrheic dermatitis was demonstrated in a phase IV clinical trial;[18] marked improvement in mean target lesion erythema, scaling and pruritus was seen 4 weeks post treatment and maintained or further improved by 8 weeks.

While presenting enhanced penetration and permeation compared to other vehicles, foams also present a distinct application advantage and increased patient compliance. Foams are generally less dense and thus easier to apply and spread on the skin surface. This property has important clinical applications in disease states where the skin is overly inflamed or sensitive, as minimal mechanical sheering force is required to disperse the formulation. Foams are also easily applied to hirsute areas with ability to penetrate the stratum corneum via the hair shaft. These findings are supported by a variety of studies assessing patient vehicle preferences.[14,19,20]

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Emerging Carrier Platforms for Topical Drug Delivery

New topical drug carrier systems allow for improved dermal localization of bioactives into the affected skin region while overcoming many of the drawbacks of conventional therapeutics. Conventional topical therapies often have limited efficacy given the variable and unspecific nature of their penetration; furthermore, a high concentration of active ingredients is often required to achieve a sufficient efficacious dose due to their low efficiency in drug delivery. These therapies also have significant drawbacks including negative sensory attributes such as greasiness, residue and difficulty of application.[21] Recent innovation of topical therapeutics has allowed for the development of new carrier systems that can optimize skin penetration and reduce the undesirable application affects associated with topical delivery. There are a variety of carrier platforms that have been extensively studied in the literature and available for consumer use.[22] Below we have outlined a review of some common carrier platforms for topical drug delivery.

Liposomes

Carriers such as vesicles are of particular interest for topical treatment of skin disease to improve the therapeutic index. Liposomes are vesicles formed from spherical phospholipids. The phospholipid bilayer, analogous to biological cell membranes,

confers liposomes amphipathic properties, enabling encapsulation of hydrophilic and hydrophobic drugs.[23] Liposomal carriers increase drug stability, enhance their therapeutic effects, and promote uptake of the drug into target tissues.[23,24] Given the instability of liposomes within aqueous solutions, Ning et al. prepared clotrimazole-containing proliposomes for vaginal application. These prolipisomes were found to be capable of sustained release for 24 hours and efficacious against *Candida albicans* as seen by a decrease in colony forming units by day 7.[25] Multilamellar vesicles are even capable of depositing a high concentration of finasteride in the follicular region for the treatment of androgenic alopecia.[26] Pornpattananangkul et al observed that liposomal lauric acid was able to fuse with bacterial membranes, effectively eradicating *Proprionibacterium acnes* infection in a mouse model, with minimal toxicity to unaffected skin.[27] Further *in vitro* and *in vivo* studies evaluated the effect of fluconazole-loaded liposomes; authors found a higher accumulation of drug following liposomal gel application compared to control, with a significantly higher retention within the stratum corneum.[23] The ability of liposomes to penetrate the epidermis may be explained by their lipid composition, facilitating greater penetration compared to other vehicle forms. It has also been proposed that the lipid matrix is able to intercalate with skin lipids, enabling loosening of the encapsulated drug and thus accelerating its release.[22] However, despite their improved permeation, confocal microscopy found that liposomes were confined to the stratum corneum and unable to penetrate the granular layers of the epidermis.[28]

Microspheres

Microspheres are another technological approach to deliver low-dose sustained release treatment to control a variety of skin disease. Microsphere technology eliminates the rapid delivery of highly concentrated drug to the application site, allowing for the sustained release of active drug. Microsphere technology effectively traps the active ingredient at the skin surface, enhancing drug delivery at the application site while limiting systemic distribtion.[29] While retinoids and benzoyl peroxide are extremely effective in controlling acne vulgaris, therapy-associated irritation is a serious complaint that limits patient compliance.[30] Eichenfield et al demonstrated a statistically significant reduction in the number of noninflammatory acne lesions after treatment with tretinoin microsphere 0.04% gel compared to empty vehicle.[31] In another study, there was no significant difference in tolerability (ie, erythema, dryness, itching, stinging) of the same microsphere drug when compared to tretinoin 0.025% cream applied to healthy skin, despite the increased concentration of tretinoin in the drug of interest.[32] Furthermore, topical microsphere-based fluorouracil, has proven effective in the treatment of actinic keratoses (AK) with a significant reduction in AK lesion counts and lesion clearance compared to vehicle control.[29] There are currently a variety of topical microsphere formulations on the market, each with increased efficacy and reduced irritability compared to traditional vehicles.

Nanoparticles

Nanoparticles are another innovative carrier being investigated and used in skin disease to harness potent drugs, allow for targeted drug delivery, and minimize systemic side effects.[33] Given their high surface-to-volume ratio, small size and stability, nanoparticles are able to surpass barriers, penetrate the stratum corneum and accumulate at target sites.[34,35] There are multiple pre-clinical programs in dermatology evaluating the utility of these carriers. Friedman et al encapsulated and enhanced the efficacy of benzoyl peroxide, finding improved antimicrobial efficacy against *P. acnes* at lower concentrations compared to native benozyl peroxide with less toxicity to eukaryotic cells.[35] In an *in vivo* murine MRSA intramuscular abscess study, which compared the efficacy of topical and intralesional nitric oxide releasing nanoparticles (NO-np) with systemic vancomycin, all treatment arms accelerated the rate at which the abscesses improved clinically. However, topical and intralesional NO-np significantly decreased bacterial survival as determined by tissue cultures as well as by histology, which demonstrated less inflammatory infiltrate and muscle necrosis as compared to other groups.[36] A spherical nucleic acid carrying gold nanoparticle (SNA-NC), when mixed with a commercial moisturizing cream (aquaphor), allowed for topical delivery of gene-targeting therapeutics into deep layers of the skin without barrier disruption.[37] SNA-NC was capable of freely penetrating into keratinocytes, mouse skin and human epidermis in concentrations sufficient to induce morphological change via EGFR gene knockdown, an important signaling molecule in epidermal cell proliferation and frequently overexpressed in malignancy.[37] Lastly, nanotechnology is allowing topical delivery of botulinum toxin, with reported similar effects to its injected formulation.[38] A purified 150kD botulinum toxin combined with a peptidyl macromolecule transport system, a combination permitting transepidermal flux of toxin into the dermis, was applied to subjects with moderate-to-severe lateral canthal lines, revealing significant improvement in wrinkling compared to placebo at both rest and smile.[39] Together, these investigations highlight nanoparticle systems as a promising new approach for targeted drug delivery, one which can hopefully combat difficult to treat dermatologic conditions and improve drug efficacy and patient compliance.

Conclusion

While topical drug delivery is a pillar of dermatologic therapy, the choice of vehicle is a crucial decision that can significantly alter efficacy, outcomes and patient compliance. An effective topical management program is dependent on the properties of the vehicle—physical chemistry, ease of applicability and penetration of drug. Topical treatment of skin disease allows for local delivery and rapid absorption of a high concentration of active drug; however, the skin's intrinsic function, to counteract the penetration of foreign substances by creating a physical barrier from the external environment, makes drug

delivery extremely complex. Conventional vehicles may complicate treatment due to their unpleasant application. Given that patient preferences impact compliance, the choice of drug vehicle will influence the observed outcome. The recent interest in particulate drug delivery systems is a promising new strategy to improve penetration while limiting systemic side effects. Therefore determining the appropriate vehicle is essential, allowing the clinician to exploit different properties of the formulation to enable enhanced penetration, improved patient compliance and increased efficacy.

Disclosure

The authors have no conflicts of interest to declare.

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