Optimizing Acne Therapy With Unique Vehicles

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ABSTRACT

The science of cutaneous drug delivery is focused on overcoming the major force of resistance to drug penetration and permeation—the stratum corneum. Acne vulgaris is a multifactorial disease of the pilosebaceous unit, resulting from abnormalities in sebum production, follicular epithelial desquamation, bacterial proliferation and inflammation. Topical treatment of even mild-moderate acne requires combination topical therapy, yet often systemic therapy is needed to ultimately confer an acceptable clinical endpoint. New delivery systems have emerged in response to the limited routes of entry and therefore efficacy of topical regimens. The unique physical and optical properties of micro/nano encapsulation of known therapeutics such as benzoyl peroxide and tretinoin allow for both improved efficacy while minimizing issues of compliance and adverse events. Vehicles that offer both inherent biological reactivity and permeation enhancement have also been shown improvement over the current armament of topical drug delivery. This current and exciting path of topical drug development will likely be continued with investigative vigor.

INTRODUCTION

The stratum corneum is arduous impediment to topical drug delivery, making localized therapy a challenge. The hydrophobic barrier of stratum corneum, the "brick and mortar" of the epidermis, places special demands on compounds intended for this unique target. The impenetrability of stratum corneum is in part due to the insoluble nature of corneocytes—a state resulting from extensive cross linking of both the cell envelope and intracellular proteins.[1] Most topical drugs cannot cannot even bypass this outer barrier, let alone pass from one epidermal layer to the next. However, both the active ingredient and/or solvent can be altered to enhance delivery to the target site.[2]

To further understand the complexities of topical drug delivery, several key terms need defining as they are often used interchangeably. First, penetration refers to the entry of into a particular skin layer, whereas permeation refers to a compound moving from one skin layer to another. Absorption, a term often used to describe various avenues of therapeutic uptake, actually is defined by the topically applied drug being taken up by blood vessels in the skin in order to enter systemic circulation.[1] However, systemic absorption is usually not the intended endpoint, rather topical therapy is generally used by the physician to provide high local impact without the potential side effects associated with, for example, an injectable or oral route of administration.

Structure and Function of the Skin

The skin is an extraordinary organ, serving numerous functions ranging from barrier protection to overseer of fluid/electrolyte homeostasis.[3] The skin is divided into three distinct yet intertwined levels: epidermis, dermis and panniculus. The epidermis is composed of stratified, squamous keratinizing epithelium, which gives rise not only to the outermost protective layer, the stratum corneum, but also is the source of several key cutaneous structures such as the pilosebaceous units, the nails and sweat glands. The stratum corneum can be considered the gatekeeper with respect to permeation of compounds into the body. The stratum corneum consists of the anucleate, fully keratinized corneocytes glued together by various epidermal lipid components, which provides for the "brick and mortar" analogy.[4] With this in mind, it is easy then to appreciate that topical therapy is literally coming up against a brick wall.

With respect to penetration, transport of topically applied materials occurs across the stratum corneum in largely passive diffusion and is reliant on the physiochemical properties of the permeating agent.[5] There are two major routes through which this diffusion across the skin can occur. The first is transappendageal, relying of the natural imperfections in skin integrity associated with hair follicles, and sweat glands. These openings can potentially allow topicals to bypass the low diffusivity of the stratum corneum.[6] Furthermore, this route may aid in the delivery of charged ions and large polar molecules that generally are slow to permeate through the stratum corneum. Ultimately, the choice of vehicle will affect its ability to utilize transfollicular penetration. The second pathway is through the epidermis itself, and is subdivided into two potential avenues, transcellular and intercellular.[4] Hydrophilic compounds are likely to flow through the transcellular route, while lipophilic materials are preferential for the more round about intercellular route. It is believed that the latter pathway is the predominant route of entry for most topical therapies.[7] Unfortunately, this pathway also serves as an impressive impediment for therapeutics intended for topical delivery.

Topical Acne Therapy: Breaking Through the Wall

Acne vulgaris is a multifactorial disease of the pilosebaceous unit, resulting from abnormalities in sebum production, folli-

cular epithelial desquamation, bacterial proliferation and inflammation. The major classes of therapeutic agents are topical and systemic retinoids, antimicrobial agents and systemic hormonal drugs. Most dermatologists rely on a combination of topical therapies, or topicals with systemic therapies to treat acne, as no single topical acne therapy is effective in addressing all of the etiologic factors. Even with the combination of a retinoid with benzoyl peroxide (BPO), together attacking likely all four of the pathogenic features of acne, penetration of said products can limit efficacy. Strides have been taken to enhance the current armament of topical therapies through novel delivery vehicles.

Benzoyl Peroxide (BPO)

BPO is an organic compound in the organic peroxide family. It consists of two benzoyl groups joined by a peroxide group, with a structural formula of $[C_6H_5C(O)]_2O_2$. It is a lipophilic material, which serves as a boon, as it can localize in the lipid rich sebaceous follicles. Current BPO formulations are emulsions, which unfortunately have some limitations. These micronized solid particles, ranging from 5–1000 µm in size, are fairly large particles with poor solubility, ultimately resulting in diminished chemical activity. These formulations lack homogeneity in terms of consistency of the dissolution of particles throughout the formulation, and contain large clusters of BPO, providing for poor penetration and unsightly cosmesis following application. On electron microscopy the surface of the skin after application of a generic current BPO emulsion demonstrated poor penetration and extensive residual product on the skin surface.

Benzoyl Peroxide (BPO) – New Vehicular Formulations

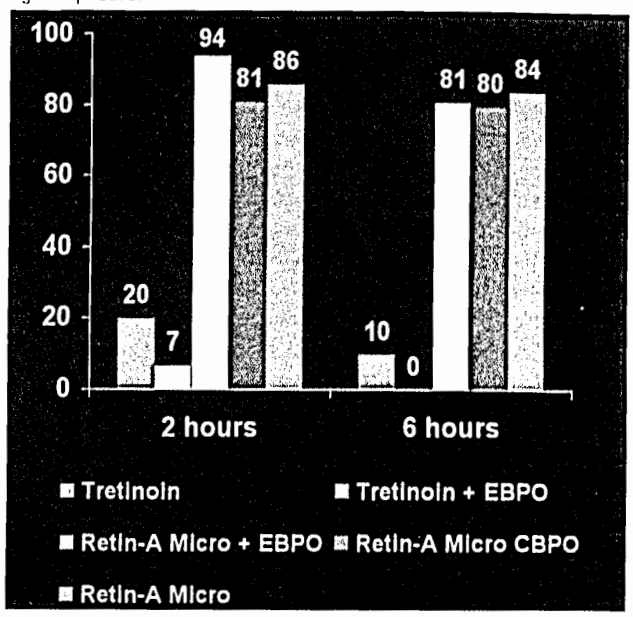
In order to combat this deficiency, solubilized BPO has been formulated, providing solid individual BPO molecules (~10^{-4} µm) in solution. Solubilization is a chemical process which occurs before the BPO is incorporated into final product. This solubilized BPO formulation has both lipophilic and hydrophilic attributes, which aim to enhance penetration into the follicle and dissolve in sebaceous secretions.

A second direction involves encapsulation of BPO in a Microsponge® delivery technology, designed to reduce irritation associated with this active ingredient. Microsponge technology has been used in the past to successfully deliver topical treatments, such as Retin-A Micro® and EpiQuin® Micro. In one study, it was demonstrated that BPO encapsulation in microsponges maximized the amount of time an active ingredient was present on skin surface or within epidermis with minimal penetration of active ingredients through the dermis.[8] This delivery system was also shown to enhance safety profiles by reducing irritancy potential while maintaining efficacy and extending product stability. Improved product aesthetic properties were also noted by the investigators.

Taking this a step further, the success of the applies BPO Microsponge® delivery system was investigated as a "wash-off" rinse. Clearly, a product such as this would only be relevant if the product displays substantivity—meaning it remains on the skin after rinsing. The persistence of effect is determined by the degree of physical and chemical bonding to the surface. Via confocal microscopy imaging, it was shown that wet skin areas treated with microsponge wash for 10–20 seconds then washed and dried had retained product within the follicular ostia. It was also found that this technology lived up to the name "sponge," as the particles absorbed twice their own weight in sebum substrate. Recall in acne, there is an increase in sebum production from the multi-lobular sebaceous follicle. This excess sebum production can be due to a change in the response of the pilosebaceous follicle to androgen stimulation, increased androgen circulation, or to both in combination.[9] One of the interesting features of the microsponge polymeric porous particles is that, as they deliver the active ingredient, they in turn absorb excess surface sebum from the skin. In head-to-head comparisons, microsponge outperformed other conventional cosmetic ingredients used as oil absorbers for sebum.

As mentioned early, combination therapies have been the mainstay of topical therapy in order to address all pathogenic features of acne. So too can combination therapy be pursued to optimize the physical state of active ingredients in the formulation. Lower concentrations of potentially irritating active ingredients can be used when incorporating a compatible moisturizing and drug delivery optimizing agent. For example, combinations of clindamycin and BPO have been inves-

FIGURE 1. Tretinoin micro is stable alone and in combination after UV light exposure.



tigated.[10,11] Clindamycin/BPO fixed combination gel formulations were evaluated in a 21-day cumulative irritation study. This single-center, evaluator-blind phase 1 study in 35 healthy human volunteers assessed the cumulative irritation potential of formulations containing clindamycin phosphate 1.2% (CP) in combination with different concentrations of BPO. Test formulations (5% BPO/1% CP, 2.5% BPO/1% CP and 1% BPO/1% CP) were applied under separate occlusive patches on the backs of subjects three times a week for three weeks. Sodium lauryl sulfate 0.3% was used a positive control. Each test application site was observed 48 hours (72 hours on weekends) post-application for signs of irritation or inflammation (a total of nine evaluations). Assessment of skin irritancy was on a scale of 0 (no sign of irritation) to 4 (erythema with edema and blistering). A total irritation score for each subject and formulation was calculated by summing each of the subject's scores on each of the nine evaluation days. The mean cumulative irritation score for each test formulation was calculated as the sum of all subject's total irritation scores for a test formulation divided by 297 (nine evaluations x 33 subjects evaluated).

Based upon the total irritation scores, all of these formulations were classified as slightly irritating under the occlusive test conditions. There was a 33% decrease in mean score the concentration of BPO from 5–2.5%. The benefits of further reducing the BPO concentration to 1% were surprisingly minimal. Overall, cumulative irritation scores increased in a dose-dependent manner with increasing benzoyl peroxide concentration, which is hardly surprising as this was described over 30 years prior.[12] Therefore, it is clear that the development of delivery vehicles aimed at increasing penetration while decreasing irritation will continue to be the focus of novel acne therapies.

Tretinoin

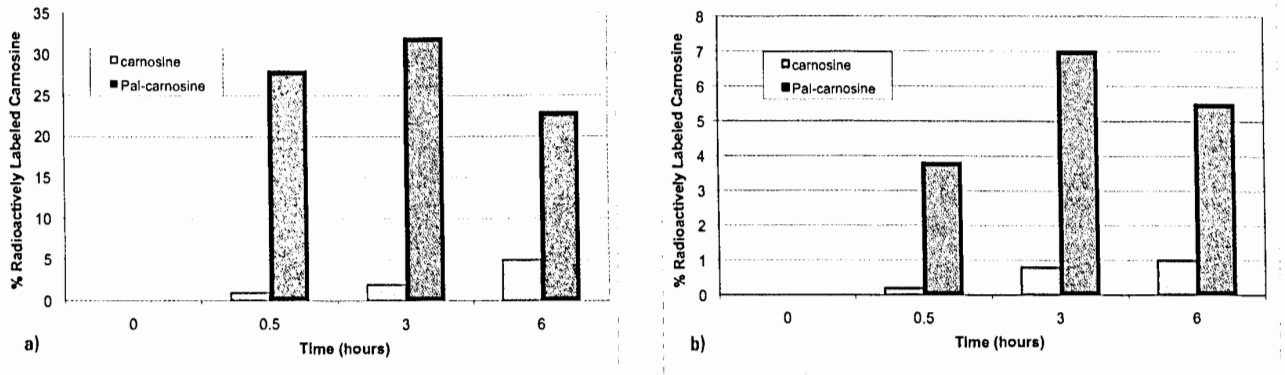
For nearly 30 years, topical vitamin A acid or tretinoin has been the mainstay for condone targeted therapy.[13] Tretinoin efficacy is directly related to its ability to induce comedolysis and normalize the maturation of follicular epithelium in order to prevent future comedone formation.[14] Although extremely efficacious, use can, similarly to BPO, be limited due to skin irritation. In addition, native tretinoin is photolabile and puts constrictions on dosing schedules. Therefore, a means to reduce these limitations has been pursued. A microsphere polymeric technology, allowing for controlled drug delivery onto the skin over time and in response to a trigger[15,16] was developed for topical tretinoin. The system itself consists of porous microspheres that mimic a true sponge in structure and function. Each microsphere is formed by polymeric "ladders" that wrap around one another, forming multiple interconnecting spaces that serve as reservoirs for the drug. These reservoirs open on the surface of the microsphere. The biologically inert polymers used to make microspheres have been shown to be non-allergenic, non-mutangenic, non-irritating, non-toxic and non-biodegradable. Microspheres themselves are too large to permeate the stratum corneum, and, because tretinoin is not available for absorption until it leaves the microsphere, there is a lower accumulation in the epidermis. Furthermore, it was shown that encapsulated tretinoin was less susceptible to degradation following ultraviolet light exposure (Figure 1).[16]

Vehicle Matters—Current and Future Directions

Hydrosolubilizing Agents (HSA-3™).

Metronidazole 0.1% topical gel is a once-daily formulation for treatment of rosacea. Well-controlled studies have shown that it is effective in the treatment of moderate to severe rosacea and well tolerated by varying evaluated subject types. The excellent tolerability is probably due to the gel vehicle, which consists primarily of purified water (92%). Previously, metronidazole was only available as a suspension in a cream formulation. Unfortunately, creams often produce undesirable cosmetic effects such as greasiness, incompatibility with make-up and irritation of the skin for rosacea sufferers, due to emulsifiers and other excipients.

FIGURE 2. Biopeptide aids penetration into the skin. **a)** Stratum corneum; **b)** Epidermis.



Carnosine is an amino acid.

Recently, a new gel vehicle capable of solubilizing greater concentrations of metronidazole was developed, making possible the cosmetically desirable attributes of a water-based gel that has the strength, safety and efficacy of 1% metronidazole. This stable aqueous gel formulation containing 1% metronidazole was achieved with the novel combination of hydrosolubilizing agents (HSA-3™).[17] This technology combines niacinamide, which has been shown to improve the appearance of facial skin texture by enhancing skin barrier function, Betadex (beta cyclodextrin), a complexing agent to increase the aqueous solubility of highly water-insoluble and lipophilic drugs, and propylene glycol, a well known humectant and permeation enhancer. The metronidazole 1% gel formulation assumes a unique configuration, with an exterior hydrophilic surface that generates water solubility and enhances moisturization, and an interior hydrophobic cavity than encapsulates the metronidazole molecules and increases drug solubility. The betadex creates a core that enables the solubilization of metronidazole gel 1%.[18]

Solvent Micro Particulate (SMP™)

Topical dapsone gel 5% utilizes the advanced Solvent Micro Particulate (SMP™) delivery system, which was specifically designed to deliver dapsone topically. The product is an aqueous gel containing dapsone, diethylene glycol monoethyl ether (DGME), purified water, carbomer 980 neutralized to physiologic pH and methylparaben as a preservative.

The SMP™ delivery system allows dissolved dapsone to permeate the stratum corneum to the epidermis.[19] It was found the properties of the diethylene glycol monoethyl ether (DGME) component helps facilitate permeation into the skin.[20] Transcutol™ CG DGME is a hydroscopic liquid that is freely miscible with both polar and non-polar solvents. Transcutol is considered a potential transdermal permeation enhancer due to its non-toxicity, biocompatibility with skin and excellent solubilizing properties.

Biopeptide Aloe Complex (BAC)

Biopeptide Aloe Complex (BAC) is a complex combining native collagen fragment chain comprised of three amino acids (Gly-His-Lys) to which palmitoyl is linked, and aloe peptides (Figure 2). The aloe polysaccharide is a pure aloe with a molecular weight range of 50–200 kDa with a mannose:galactose:glucose content of 40:1:1. The linked palmitoyl has both lipid and water solubility, which helps with cutaneous penetration. This material has been shown to increase fibroblast and collagen production as well as have anti-inflammatory and immune activity.[21,22]

CONCLUSION

The science of cutaneous drug delivery has fought vigorously to overcome the major force of resistance to drug penetration and permeation—the stratum corneum. New delivery systems have emerged in response to the limited routes of entry. Micro/nano encapsulation of known therapeutics and the utilization of delivery vehicles that offer both inherent biological reactivity and permeation enhancement offer patients improved results when using topical therapy. It is clear that this path of development will continue to be pursued with investigative vigor.

DISCLOSURES

Dr. Kircik is a consultant and investigator, and is on the Advisory Board, for Valeant Pharmaceuticals, Intl., Warner-Chilcott, Intendis, Amgen, Inc., and Galderma Laboratories, LP. He is an investigator, speaker, and is on the Advisory Board for Allergan, Inc. He is a speaker, investigator, consultant, and is on the Advisory Board for OrthoNeutrogena, SkinMedica, Inc., Stiefel Laboratories, Inc., and Connetics Corporation. He is an investigator, consultant and speaker for CollaGenex. He is a consultant and is on the Advisory Board for Colbar. He is a consultant for and stockholder in Johnson & Johnson. He is an investigator and speaker for Leo, PharmaDerm, UCB, and Asteilas Pharma US, Inc. He is an investigator and is on the Advisory Board for Nano Bio and Ferndale Laboratories, Inc. He is a speaker and is on the Advisory Board for Genentech, Inc. He is an investigator for GlaxoSmithKline, PLC, Health Point, LTD, Medicis Pharmaceutical Corp., Navartis AG, Nucryst Pharmaceuticals Corp., Obagi, QLT, Inc., Pfizer, Quatrix, TolerRx, Acambis, Asubio, Berlex Laboratories (Bayer HealthCare Pharmaceuticals), Biolife, Breckinridge Pharma, Centocor, Inc., Combinatrix, Coria, Dow Sciences and Dusa. He is a speaker for Innovail, 3M, Serono (Merck Serono International SA), Triax, Abbott Laboratories, and Dermik Laboratories. He is on the Advisory Board for Biogen-Idec.

Dr. Friedman has no relevant conflicts of interest to disclose.

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