On Understanding the Clinical Relevance of "Formulation" for Topical Products Applied to the Skin

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Human skin is a complex entity – it has many functions in addition to its barrier function, including temperature regulation, providing tactile, temperature, vibration sensation, moisture preservation, protection from solar radiation, and providing protection from micro-organisms. Also of interest is that the skin is an outward projection of who we are – it one of the human organs whose appearance has overt cosmetic, cultural, and societal implications.

Skin has multiple structures relevant to its many functions in addition to the layers of cells and scaffolding and stratum corneum. These include follicular units, which include hair, root, sheath, associated glands, nerves, muscle, and stem cells. It also includes underlying blood vessels, vessel smooth muscles, underlying fat. Structures and skin appearance vary depending on where on the human body we are looking.

As a licensed-to-practice dermatologist, I can appreciate the relevant role these structures or damage to structures may play in disease and normal skin health for my patients. I can also appreciate how these structures impact the delivery of drug to the putative sites of action for drugs we use to treat various skin diseases or conditions.

What are some of these diseases? Acne, psoriasis, eczema or atopic dermatitis, cold sores, alopecia, rosacea, and skin cancer are just some examples. Some of these disorders have effective systemic drug and biological therapies developed recently, however, topical drugs continue to play an important role in the integrated holistic management of these diseases.

What aspects of product formulation impact drug delivery and are in turn impacted by skin structure?

The active pharmaceutical ingredients (API) key issues are dissolution and size of the API particles. The particles themselves participate in drug release functionality for the product, but also allow for API in its undissolved state to penetrate and accumulate around hair follicles and in other dermal substructures when relevant (e.g., in acne or to treat peri-follicular inflammation).

The excipients go hand in hand with each type of API, e.g., hydrophilicity/hydrophobicity, and the target indication. The clinical mantra of "if it is wet, dry it, if it is dry, wet it" is often addressed within the formulation of drugs used to treat the target disease with appropriate excipients.

It should be noted that for topical products, excipients are sometimes misidentified as "inactive ingredients" when they play a crucial role in the treatment of the disease, including substituting as a barrier for broken skin, reducing water loss, providing a reservoir environment for the API, performing penetration functions for both drug and co-solvents, providing relief to irritation and itch, and improving the spreadability or look and feel of a product applied to the skin. Over the centuries, substitution of excipients that perform certain functions has occurred with benefit to users, e.g., substituting certain fatty acid ester mixes like Crodamol or PCL liquid for the natural preen oil (sparing the source animals and making certain topical products friendly to consumers with certain beliefs) or substituting one

thickening agent or emulsifier for another. In the context of generic drugs, this substitution should be done keeping Q3 parameters and drug availability intact.

In the context of generic drugs and comparing a test product to the reference standard, the topical drug field has evolved over the course of the last three decades from initially having an in vitro comparison of Q1 or qualitative comparison, i.e., the same ingredients, considering grade and morphology of the ingredients being put into the formulation; Q2 or quantitative comparison, i.e., the same relative amount of each ingredient which might have some variation due to measurement capabilities or variation in batches; and adding in Q3 or physicochemical and structural difference evaluations in the early 2000s, e.g., rheology, API characteristics in the manufactured product as applied to the skin, pH, "spreadability", etc. The keys to matching Q3 are considerations for variations in Q1, possible slight but allowable differences in Q2, and, most importantly, manufacturing and packaging processes that lead to the final marketed formulation. Differences in manufacturing can include intensity of mixing, temperature at which mixing is done, the order of addition of the excipients and API, the introduction of unique aspects that could impact final physicochemistry and structure, API bioavailability, and look-and-feel or sensorial attributes of the final product.

For indications like acne vulgaris, the site of action may be at the root of the hair follicle, i.e., providing anti-microbial, anti-inflammatory, and anti-keratinization, thus requiring API access to the site action. In general, matching Q1, Q2, and Q3 will help us arrive at a bioequivalent test product. As we develop the science of understanding the relevance of certain Q3 attributes this may evolve. For example, particle size may not need to be entirely matched but could possibly be related to having a proportion at a certain size cut-off and in a certain localized concentration to allow the drug to work effectively. Currently, we do not know what that size cut-off is. This may be further complicated by the need to reduce adverse events such as irritation which would have an adverse impact on frequency of application and patient dosing. For these reasons, at this time, if there are variations in Q3, clinical endpoint studies may still be needed. For indications like cold sores, it may be film-forming ability of the formulation that allows for a therapeutic protective layer over an open sore. For diseases where the chronic response to inflammation might be stratum corneum thickening, it may be important to have sufficient skin penetrating solvent to carry dissolved API, a Q3 approach together with dissolution (IVRT) and skin penetration assays like IVPT may be sufficient as proof of bioequivalence (BE).

For topical dermatological products, it is not always necessary (legally, regulatorily, or practically) for products to be Q1, Q2 to have the same bioavailability or same performance as has been shown in the past with approved ANDAs (some of which have utilized a comparative clinical endpoint approach to BE). Q3 sameness may at this time in our generic drug regulatory evolution be a stand-in for comparable performance, but as we learn more about what Q3 aspects are necessary for each target indication, the relevant sets of data will be tweaked.

In summary, it is important to understand the disease and skin location to which the product is applied and the site of action of the drug under consideration. With appropriate application of analytical and measurement science we can get to "Yes" for BE in more ways that are valid, appropriate, and clinically responsible.