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Conference Report

Principles and Criteria in the Development and Optimization of Topical Therapeutic Products

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CONTRIBUTORS

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INTRODUCTION

The overall purpose of the Topical Therapeutic Products Workshop, held March 26–28, 1990, in Crystal City, Virginia, was to review the relevant literature and discuss the problems and issues in the development and optimization of topical therapeutic products in order to define the state of the art of formulation practice. The workshop, cosponsored by the U.S. Food and Drug Administration (FDA) and the American Association of Pharmaceutical Scientists (AAPS), was coorganized by scientists from the FDA, the AAPS, academia and the pharmaceutical industry (Appendix 1). An important goal was to establish a consensus on the present problems in measuring topical drug delivery. It is hoped that these problems can be addressed in the subsequent workshops.

The major objectives of the workshop were as follows.

- To review and evaluate available information of topical drug products.
- To evaluate relationships among pharmacological activity, drug delivery, and clinical efficacy.
- To identify ways to optimize topical drug delivery to target sites.
- To identify important principles in the development and optimization of topical drug products.
- To raise possible concerns related to the local and systemic toxicity problems arising from optimization of drug delivery.
- To discuss regulatory concerns in the evaluation of topical drug products.

At present, there are no guidelines with regard to drug delivery and the assessment and use of laboratory models (including animals and mathematical) to predict and optimize the clinical efficacy of topical drug products. The present guidelines for bioequivalence assessment suggest studies with clinical end points. It is not always practical to conduct these studies. It is hoped (1) that a greater understanding of how to conduct systematic and scientific studies to optimize topical products will emerge (other than studies with clinical

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end points), so that (2) more reliance can be placed on the use of laboratory studies, including those involving the use of animals and *in vitro* studies with animal and human skin and synthetic membranes, to understand, develop, optimize, and compare topical drug delivery systems.

DIFFERENTIATING TRANSDERMAL AND TOPICAL (DERMATOLOGICAL) THERAPEUTIC PRODUCTS

Transdermal and topical products are becoming increasingly important, and their use in therapy is getting more widespread. While topical products to treat dermatological ailments have been in existence from the earliest times, transdermal products, where the skin is used as an alternate route for systemic therapy, are relatively new therapeutic entities. Even so, the principles involved in the development and optimization of transdermal products are far better understood than those for topical products. Reasons for this are as follows.

- With transdermals, the blood concentration needed to achieve therapeutic efficacy is generally known.
- Most transdermals operate at relatively even thermodynamic activity and therefore the drug delivery kinetics of transdermals are actually less complicated than for topical dosage forms.

There has been a tendency among researchers to mix and confuse the principles of topical and transdermal delivery. It is critical to distinguish the substantial pharmacokinetic and clinical (performance) differences between topical products and transdermal drug delivery systems. Transdermal products are designed to deliver drugs through the skin to achieve systemic effects, hence the skin is not the target. A maximal net drug transport across the skin and a minimal skin retention of the drug are the optimal attributes of a transdermal product. In contrast, a topical drug product is designed to deliver drug into the skin for treating dermal disorders, and here skin is the target organ. Non-steady-state transport generally characterizes a topical drug product. Maximal efficacy and minimal exposure to systemic toxicity are among the attributes sought for an optimal topical drug product. The definitions of some additional terms relevant to transdermal and topical products also need clarification (Appendix 2).

A topical drug product is applied over the diseased skin area as a thin film (typically 1–3 μl solution/cm^2 or 1–3 mg cream or ointment/cm^2, amounting to films from 10 to 30 μm in thickness) with a rubbing action. Usually, little visible mass remains on the skin following inunction. No substantial formulation builds up on the skin surface upon repeated application, which is often once a day but may be more frequent. In most cases, the formulation is left unoccluded. This allows the formulation components to evaporate and/or be absorbed into the skin or rubbed off or sloughed off the skin. Thus, immediately upon application, the physicochemical and thermodynamic conditions which drive drug delivery change radically from when the formulation was first applied. In contrast, a transdermal system is a prefabricated device in which drug is incorporated into some sort of reservoir, in some instances a "pouch," in others a dispersion in a polymer layer, and in yet others a dispersion in the adhesive. This device or patch is fastened adhesively to the skin surface. Rarely is the matrix containing drug exposed to the atmospheric conditions. There is some conditioning of the application (patch) by insensible perspiration, but for the most part, the physicochemical and thermodynamic conditions remain constant and thus provide a nearly constant rate of drug delivery through the skin. At least one transdermal system has been designed such that the rate of drug release from the patch onto the skin surface is slower than the permeation of the drug through the skin. Consequently, this transdermal product controls the rate and extent of drug delivery to the systemic circulation.

Since the percutaneous absorption is common to both topical and transdermal products, there has been a tendency to view this event as being of comparable significance in each of these delievery modalities. Therefore, mistakenly, the sole basis of drug delivery performance has been the drug flux across the skin, without proper regard for the disposition of the drug in the local tissue.

For a transdermal product, an optimal drug flux across the skin without appreciable drug buildup in the skin is ideal. For topical (dermatological) products, an optimal drug buildup in the skin with little or no drug flux through the skin is most ideal. Since the drug concentration rarely remains constant in the case of a topical formulation applied on the skin, the situation for dermatological products is far more complicated than seen with most transdermal drug delivery systems. Topical formulations usually contain several excipients; these also partition into the skin in accordance to their physicochemical properties. Certain excipients change the integrity of the stratum corneum. When this occurs, the solubility of compounds within the horny layer and/or the ease with which they diffuse through this tissue are affected. Some components including drugs (e.g., nitroglycerin) occasionally evaporate away in the course, systematically altering the drug's activity in the remaining vehicle. For unstable drugs, exposure to air and light can be a problem. Given such issues, drug delivery into and retention in the skin are not well reflected by steady-state flux data. This means that drug localization within the skin depends upon the unique properties of the formulations and may not relate well to *in vitro* flux data as measured, for example, in diffusion cells. Depending upon the specific formulation used, high drug accumulations in the skin may be achieved even at low flux values. Consequently, it is critically important that the topical drug delivery be viewed differently from transdermal delivery. In particular, emphasis should be placed on drug retention in the skin for dermatological products as opposed to drug flux across the skin for transdermal delivery systems.

PROBLEMS IN THE DEVELOPMENT AND OPTIMIZATION OF DERMATOLOGICAL PRODUCTS

Pathophysiology of the Skin and Target Sites

The pathophysiology of the skin and its effects on the barrier properties of skin are quite relevant to the understanding of topical drug delivery. Thus, only with a thorough mechanistic understanding of the drug uptake process can optimal drug delivery systems be designed. This knowledge is necessary in establishing models to evaluate formulations.

In particular, in animal models the skin should have drug uptake properties which are comparable to those of the human skin condition which is to be treated. An animal model can be considered only predictive under these conditions.

Another important consideration is the site of action of a drug in the skin. Drug delivery from topical products should ideally be directed to specific skin targets within its multiple layers to be optimally effective. However, targeting of drugs to a particular cutaneous tissue, e.g., the basal epidermis or fibroblasts in the dermis, cannot be accomplished without also involving surrounding tissues, and thus an effective and sustained rate of delivery needs to be sought to provide optimal therapy. Ideally, one would like to deliver the exactly correct amount of drug exclusively to specific cellular targets. Drug targeting to specific cells within the skin structures promises to be an extremely complex issue, which is without precedent to date. The problem is complicated by the fact that, for many dermal conditions, the target sites and local mechanisms of drug action remain unknown.

A greater knowledge of all aspects of skin pharmacology will assist in the development of meaningful approaches here. Close working relationships among drug delivery scientists, pharmacologists, toxicologists, and clinical scientists are essential for developing target-specific dermatological products.

Screening of Drugs and Their Derivatives for Relative Pharmacological Activities

In the predevelopmental phase for new chemical entities, many drugs and derivatives are screened for relative pharmacological activities. Generally a simple vehicle, often acetone, is used as the solvent in the screening process, without due concern about the effects vehicles have on drug delivery. This approach presents the risk of selecting suboptimal compounds or rejecting potentially effective compounds in the screening process. A better approach would be to develop a first-generation formulation with an eye to the physicochemical properties of the drug candidate and delivery aspects to the target disease.

The Developmental Process for Dermatological Products

Some of the key decisions and activities specific to developing a drug into a marketable topical product are as follows.

- Selecting the dosage form(s) most suited to treating the disease or condition. One or another of a cream, ointment, lotion, solution, gel, spray/aerosol, plaster, etc., might be most appropriate in a given situation.
- Preparing prototype formulations.
- Developing analytical methods to assay drug in the formulations and in the skin layers.
- Assessing drug uptake in skin and percutaneous transport *in vitro* and/or *in vivo*.
- Assessing the potential for cutaneous toxicity (e.g., irritation, sensitization).
- Microbial testing and selecting formulation preservatives.
- Testing for cosmetic/aesthetic qualities.
- Performing Phase I, II, and III clinical studies.
- Scaling up for large-scale manufacturing, preparing stability batches, and developing process documentation.
- Developing appropriate quality-control tests.

Quite often, drug formulations for clinical testing are selected without due consideration of optimization of drug uptake/retention in skin. Formulation development is not conducted by optimizing drug delivery to the target site, despite the fact that this may be pivotal to the success of a topical product. In some cases, formulations are evaluated for the drug flux across the skin, and the formulations exhibiting maximal fluxes are selected for further testing. The correct criterion for selecting optimal formulations of topical drugs, however, should be achieving optimal drug uptake/retention in specific regions of the skin, and not necessarily high flux per se. These two parameters, retention and flux of a drug, may or may not be related. When a topically applied drug is ineffective in clinical trials, we presently cannot determine whether it is inherently inactive or whether its delivery was insufficient. Knowledge of the drug's local tissue concentration offers a parameter which can be used to make this differentiation and to optimize the formulation further and reevaluate it for clinical efficacy. Unfortunately, rarely, if ever, do we know the effective drug concentration in the skin. It is hoped that as we learn more about the developmental aspects, we will find ways to fill in such a critical knowledge base. Meanwhile, in the absence of such information, the prudent developmental scientist should pursue all reasonable means to optimize skin uptake/retention before evaluating the clinical activity of the drug. The following issues and questions should be raised during the developmental process for topical drug product.

- Are the physicochemical properties of the drug in question sufficiently well understood?
- Has the pharmacological activity of the drug been either demonstrated or adequately predicted?
- Are the pharmacological models used in assessing/predicting the drug's pharmacological activity relevant and well conducted?
- What research vehicles were used in screening the drug for pharmacological activity? Were these relevant and appropriate?
- Is the target tissue for the drug known? Is this the epidermis, the dermis, or some specific cellular group within these strata?
- Have drug delivery and, specifically, drug uptake/retention within the skin's layers been adequately evaluated?

CRITICAL CONSIDERATIONS IN DRUG UPTAKE STUDIES IN SKIN AND CORRELATION WITH CLINICAL EFFICACY

Drug Uptake Studies in Skin

The critical issues involved in conducting drug uptake and retention studies in the skin for topical formulations include the following.

- *What experimental tissue should be used?* In *in vitro* studies should human cadaver skin or animal skin be used? This is still an area of research and exploration.
- *Should studies be* in vitro *or* in vivo, *and in what*

circumstances? Information is needed to establish the correlation between data on drug retention in skin for *in vitro* and data for *in vivo* studies.

- *What are the time dependencies of local drug delivery and retention?* How does the dosing regimen affect the retention of a drug in the skin? The kinetics of drug retention from single- and multiple-dose applications are important and should be given critical consideration in deciding the dosage regimen of the product. For evaluating new drugs for clinical efficacy, a knowledge of drug retention kinetics may be important in designing clinical protocols.
- *What techniques are best for evaluating drug uptake in the skin?* A review of the literature indicates that several types of apparatuses and procedures are claimed to be useful in conducting drug permeation and, in some cases, drug retention studies in skin. The tendency has been to use steady-state permeation procedures for topicals, though these are only really interpretable in the instance of transdermal products. Generally, for topical products, finite-dose procedures should be employed and a formulation should be applied at a level of 1–3 mg or μl of the product/cm^2 of skin, usually with inunction. The skin should be left open to the atmospheric conditions if this mimics the clinical use situation.
- *How does cleansing the skin surface affect apparent drug delivery and retention?* The cleansing procedure is another critical experimental variable which needs a research definition. Typically, a formulation is applied on the skin as a finite dose. After a certain time, excess formulation is removed from the skin surface before determining the drug levels in the skin layers. There is no uniform, validated procedure for achieving this purpose. Rather, the procedures include washing the skin with (1) small portions of volatile solvents, such as methanol, ethanol, or acetone, or (2) aqueous solutions of detergents. The possibility that such cleansing procedures will influence the experimental results is real, considering that most of the drug applied on the skin normally remains on or, at least, near the skin's surface. Therefore, even a slightly incomplete wash can mean a large error in estimating skin retention. On the other hand, a procedure that is too vigorous runs the risk of extracting drug which otherwise would be retained in the skin layers. A validated wash procedure needs to be developed for use in drug retention studies in skin.
- *What analytical procedure is to be used?* Another critical issue is to develop a specific and sensitive analytical procedure, preferably one which is chemically specific such as HPLC, for determining low levels of drug in the epidermis or dermis. Radioisotopic methods may be used, but one must recognize that these are not favored for human research and often lack molecular specificity.
- *How should data be presented?* Data presentation and interpretation also become critical issues. There are no established precedents for analyzing skin retention data. Should retention results be expressed in terms of the amount of drug per unit area of the skin or in terms of the amount of drug per unit weight of the respective skin layer? The latter makes more sense because it is the drug concentration which is important and related to pharmacological activity. One would thus need to know the masses of the skin's layers. Stratum weights depend on several factors including age, gender, weight and the anatomical site of the human or animal used. For data reproducibility, controls may need to be placed on these factors. On the other hand, in conducting drug uptake studies in humans using skin stripping procedures, results are often expressed as amount per unit area. However, expressing results in terms of drug amount per unit weight of the skin layer is desirable.
- *What are the influences of formulation, application, and subject factors on drug delivery?* The effects of some pertinent factors such as drug concentration, total dose, thickness of application, pH of the formulation, drug lipophilicity, vehicle lipophilicity, temperature, hydration/occlusion, and patient's age/gender/anatomical site on retention of drugs in skin deserve extensive study.

Use of Enhancers

A review of the literature might lead one to conclude that enhancer effects are well studied. However, most of these data pertain to the enhancement of flux or permeation across the skin, a parameter of direct importance for transdermal products. How enhancers affect the local deposition of drugs, on the other hand, is not well-known and studied. It is important that enhancement for topical products be studied for drug retention in the skin, as enhanced permeation does not necessarily mean that there will be better targeting of the drug. As mentioned earlier, permeation is not a relevant parameter for the optimization of topical drug delivery.

Clinical Correlations

How drug retention in the skin relates to clinical efficacy is another important consideration in drug uptake studies in skin. In principle, since a dermatological drug is meant to ameliorate a skin disease, optimization of the drug uptake/retention pattern in the skin should provide an optimal therapeutic effect. However, there are no explicit examples to prove this contention. Gathering such information not only will produce optimal products, but also will assist in learning about the specific target sites. Clinical efficacy may vary with drug retention in the skin in a linear or asymptotic manner. If the profile is linear, the product can still be further optimized. On the other hand, if a plateau is reached in clinical efficacy, further optimization of drug retention in skin is unnecessary and, indeed, may increase the risk of local or systemic toxicity.

REGULATORY CONSIDERATIONS

Bioavailability and Bioequivalence Issues

The issues of bioavailability and bioequivalence were given considerable thought at the workshop. Since the target

organ for topical products is the skin, it seems logical that determining drug concentrations in the skin layers should provide an assessment of topical bioavailability. Preliminary work on glucocorticoids indicates that the drug concentration in the stratum corneum (obtained by the skin stripping technique) can be correlated with the pharmacodynamic response and that the drug concentration may be used to estimate the bioavailability of the product. More work in this area is needed to establish procedures for assessing bioavailability of topical dermatological products. Using the skin stripping technique, only the stratum corneum is easily accessible and the deeper tissues, e.g., the viable epidermis and dermis, are not accessible. The skin stripping technique thus is subject to criticism that, in many cases, the drug concentration at the site of action is not measured and may not correlate with the bioavailability and bioequivalence of topical dosage forms.

At present, there are no accepted nonclinical models or approaches to predict or determine the bioavailability and bioequivalence of dermatological drugs. Consequently, bioequivalence assessment of test and reference products is based on studies with clinical end points or pharmacodynamic measurements such as the blanching assay for glucocorticoids. This raises the problem of how to ensure bioavailability and bioequivalence where (1) minor formulation changes are involved and (2) process changes are involved during scale-up. Can *in vitro* and/or *in vivo* drug uptake studies in skin answer these questions? Reliable data are not available to support any such approach. Using a theoretical approach, it may prove possible to develop mathematical models to predict drug retention based on experimental information for a given drug. This so-called C^* approach (drug concentration at the target site) is worthy of further pursuit.

Quality-Control Issues

At present, no recognized quality-control procedure is available for assessing batch-to-batch uniformity of dermatological products in terms of drug release. A simple procedure to determine the drug release rate from the cream formulations using commercially available diffusion cells and synthetic membranes has been suggested as a means of accomplishing this, but it is clear that this approach needs to be carefully validated before it can be recommended and widely implemented.

Since drug must first be released from the formulation and then permeate through the stratum corneum for therapeutic effect, it may be appropriate to use drug release properties using synthetic membrane techniques as a quality-control test to ensure batch-to-batch uniformity. The quality-control test should be able to detect formulation or process factors which may affect the bioavailability and bioequivalence of the drug product.

APPENDIX 1

Topical Workshops Planning Committee

Steering Committee (Cochairmen)

Distinguished Professor William I. Higuchi (University of Utah)
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Dr. Howard I. Maibach (University of California at San Francisco)
Dr. Gerald G. Krueger (University of Utah)
Dr. Hans Schaefer (CIRD Galderma, France)

APPENDIX 2

Terminology

Permeation: Net transport of drugs across the skin. A relevant parameter in transdermal drug delivery.

Retention: Drug residence in the skin or in its layers. Drug localization in the skin. A relevant term in topical drug delivery.

Permeable: Capable of being permeated, e.g., skin 1 is more permeable than skin 2. Also, capable of permeating the skin, e.g., drug 1 is more permeable than drug 2.

Retentive: Capable of retaining substances in the skin. Also, capable of being retained in the skin.

Permeability: A quantifiable term which describes the degree to which a skin is permeable.

Retentivity: A quantifiable term which describes the degree to which a skin is retentive.

Permeant: A substance which permeates the skin.

Retentant: A substance which is retained in the skin.

Permease: A substance that catalyzes the permeation of another substance across a membrane. It is a more specific term than enhancer.

Retentase: A substance which catalyzes the retention of another substance in the skin.

Penetration: A term which some researchers have used interchangeably to describe drug delivery *to* or *through* the skin. It causes confusion.

Association News and Announcements

PREDICTION OF PERCUTANEOUS PENETRATION

The Third Prediction of Percutaneous Penetration Conference will take place at the Palais de Congres, La Grande Motte, Montpellier, France from April 14–16, 1993. It will provide a dedicated forum for discussion of the latest information on the penetration of compounds through skin and will therefore be of particular relevance to all scientists and clinicians involved in research, development, therapy, risk assessment, and regulatory affairs. Internationally respected speakers will address current topics of importance in the agrochemical, cosmetic, and pharmaceutical fields, and the program will include workshops and poster sessions. Initial enquiries should be addressed to Dr. Valerie James, PPP Conference, University of Wales, Redwood Building, Cardiff, CF1 3XF, U.K.; tel./fax +44 (0) 222 874952; e-mail to brain @ uk.ac.cardiff.

SYMPOSIUM ON NOVEL CONCEPTS IN PHARMACOKINETICS

This conference, will be held October 5–8, 1992, and a Satellite Workshop entitled *Convolution, Deconvolution and Linear Systems,* will be held October 9, 1992 at the Smolenice Castle in Czechoslovakia. For more information (in the U.S.) contact Dr. Peter Veng-Pedersen, University of Iowa, College of Pharmacy, Iowa City, Iowa 52242; tel. (319) 335-8792; fax (319) 335-9418. For information outside the U.S.: Dr. Tomas Trnovec, Institute of Preventive and Clinical Medicine, Limbová 14, 833 01 Bratislava, Czechoslovakia; tel. (+42-7) 374 980; fax (+42-7) 373 906.

PHARMACOKINETICS FOR PHARMACEUTICAL SCIENTISTS

The Drug Studies Unit and the Department of Pharmacy of the University of California at San Francisco, School of Pharmacy, announce its Sixth Annual, 5-day fundamental course on Pharmacokinetics for Pharmaceutical Scientists on January 31–February 5, 1993 in San Francisco. This highly rated course will emphasize up-to-date information on physiological conceptualization of and problem-solving approaches to pharmacokinetics. Presentations will be delivered via lectures and multiple small-group workshops throughout. For more information, please contact Leslie Z. Benet, Ph.D., Department of Pharmacy, School of Pharmacy, University of California, San Francisco, California 94143-0446; tel. 415/476-1680; fax 415/476-2744.

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