Review

The Bioavailability of Dermatological and Other Topically Administered Drugs

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The literature addressing determination of the bioavailability of dermatological and other topically administered drugs has been reviewed. The various methods employed, their advantages and drawbacks, have been identified and evaluated. The state of the art and the success of topical bioavailability assessment are discussed in the light of the information presented. It is concluded that, although current methodology ensures the responsible use of topical medicaments, the techniques are, on the whole, quantitatively inadequate. A number of recommendations are proposed as possible improvements to the approaches now undertaken, and specific measurements for drugs in different therapeutic categories are suggested. The ultimate objective of this survey is to catalyze the establishment of straightforward, objective, quantitative, and reproducible methods to evaluate topical bioavailability and to reduce significantly, thereby, the incidence of bioinequivalence and pharmacological inactivity observed following drug dosing to the skin.

KEY WORDS: topical drugs, bioavailability; percutaneous absorption; pharmacology, cutaneous; bioequivalence, topical.

INTRODUCTION

Application of the term "bioavailability" to topical dosage forms presents, first, a question of definition. Most simply, the bioavailability of a topical drug may be considered to be its relative absorption efficiency (1–4). Unfortunately, a very general definition such as this begs a further series of questions: Absorption efficiency relative to what? Relative to another drug, to the same drug administered via a different route, or to the same agent delivered from a standard vehicle preparation? Absorption where? To the stratum corneum, to the epidermis or dermis, or into the systemic circulation? The subject is clearly complex and is characterized by an absence of consistency in approach (3–7). We may state at the outset, therefore, that the straightforward concept and measurement of bioavailability for oral drug administration cannot, in most cases, be applied to topical dosage forms.

The topical delivery of therapeutic agents serves two primary functions.

(i) To treat local skin disease or discomfort. Drugs falling in this category comprise, by far, the majority of transcutaneously delivered substances.

(ii) To treat systemic disease. A limited number of drugs are currently included in this group, although there is, of course, a great deal of transdermal drug delivery research in progress.

The latter class of agents and dosage forms presents a rather conventional bioavailability problem which can be dealt with using established procedures. The former, on the other hand, confronts the generality of the bioavailability definition head-on.

Historically, the approach to the determination of topical bioavailability has centered around the evaluation of basic criteria selected (predominantly) from a choice of three:

(a) To what extent does the drug, when delivered from its topical dosage form, elicit a designated pharmacological effect?

(b) To what extent does the drug penetrate through skin tissue from the applied vehicle phase? and

(c) To what extent is the drug released from the delivery system into an appropriate receptor phase?

In practice, bioavailability is expected to be correlated with the level and duration of persistence of drug in the "biophase," which includes the site of drug action (3,8). When one considers bioavailability (F) from an oral dosage form, for example, it is generally accepted that circulating blood levels (and areas under plasma concentration–time curves, etc.) will adequately reflect the time course of drug presence within the biophase and that they can be used, therefore, to evaluate F. As we show, this approach is also acceptable for topical dosage forms in category ii above, i.e., for transdermal drug delivery systems (bandages, "patches," ointments) designed to treat disease of systemic origin. For dermatotherapeutics, however, this procedure (a) cannot be employed routinely (because circulating levels of the topical medicament are too low to be analyzed by conventional techniques) (9) and (b) is of questionable relevance because the biophase is within the skin at the applica-

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tion site (3); it becomes almost impossible, therefore, to measure drug concentrations at the site of action and show that these amounts are related to drug levels in the bloodstream. In consequence, the above approaches (a–c) have assumed major roles in the bioevaluation (bioavailability and bioequivalence) of topical drug dosage forms.

The objectives of this review are

(i) to present the pertinent literature and information concerning the evaluation of topical bioavailability;
(ii) to describe the key methods of topical bioavailability determination revealed by the literature search;
(iii) to identify those approaches, used to evaluate topical drugs, which are well validated and show acceptable reliability; and
(iv) to suggest how, in the future, the problems of assessing the bioavailability of topical drugs should be addressed.

This article addresses these aims in the following way: having identified the sources of information on which this review is based, methods for evaluating the bioavailability of dermatological drugs (and drugs delivered transdermally to elicit systemic pharmacological effects) are described. The procedures for the assessment of bioavailability are critically evaluated and their attributes and limitations are indicated. We conclude by proposing a number of recommendations which, it is believed, would significantly improve the quality of topical bioavailability determination. Finally, two appendices offer (a) specific suggestions of bioavailability measurement for drugs in different therapeutic classes and (b) a sampling of examples in the literature of topical bioin-equivalence.

INFORMATION—SOURCES AND ACQUISITION

Essentially conventional procedures were followed in obtaining the information on which this report is based. Pertinent literature searches, of course, provided the bulk of the material analyzed.

Letters stating the purpose of our efforts were mailed to approximately 100 recognized investigators working in skin penetration, dermatopharmacology, and topical biopharmaceuticals. Responses were received from a significant number of those canvassed. Replies frequently included either a list of references or reprints of relevant articles.

Finally, much attention was paid to a limited number of in-depth treatises focusing upon dermatological formulations and percutaneous absorption. These works were excellent sources of both extensive literature citations and informed comment on the subject of bioavailability. Outstanding among these are B. W. Barry’s monograph “Dermatological Formulations: Percutaneous Absorption” (3) and the review “Skin Absorption” by H. Schaefer et al. which appears in “Normal and Pathologic Physiology of the Skin” (4).

DETERMINATION OF THE BIOAVAILABILITY OF DERMATOLOGICAL DRUGS

When a drug preparation is applied to diseased skin, the purpose is to induce a therapeutic response. The occurrence of this response and its time of onset, duration, and magnitude depend upon the relative efficiency of three sequential processes:

(i) release of the drug from the vehicle,
(ii) penetration of the drug through the skin barriers, and
(iii) activation by the drug of the desired pharmacological effect.

To determine topical bioavailability, therefore, requires that we possess techniques capable of assessing these three events for the drug/vehicle combination.

Drug Release from Topical Vehicles

Release rates of drugs from topical vehicles have been well studied (10–20) despite the generally accepted fact that liberation of the medicament from the formulation is not usually rate-determining for drug penetration into the skin. Drug release studies invariably involve simple in vitro methods, extrapolation of the results from which to the in vivo situation may be questionable. For example, a classic release test may involve measurement of drug diffusion out of the vehicle into some type of “sink” receptor phase. This receiving medium may be aqueous or lipophilic (e.g., isopropyl myristate) (21–24) and may be separated from the vehicle by a model synthetic membrane (e.g., silastic). While these experiments are useful for comparing formulations under carefully controlled and reproducible conditions in the laboratory, they may bear little relation to delivery kinetics in vivo because the skin is frequently the input-rate controlling barrier. These studies may also neglect the effects that different vehicles may have on the permeability of the skin, e.g., increased hydration with occlusive ointments, or the penetration-promoting potential of low molecular weight solvents (8,25,26). Of course, in the design and formulation of a topical dosage form, considerable attention must be paid to the physical and chemical properties (stability, rheology, solubility, phase characteristics, elegance, etc.) (3). Without careful efforts to ensure that the delivery system is functional a priori, subsequent evaluations of topical bioavailability may prove futile.

Methods for Studying Percutaneous Penetration

The measurements, which are made most frequently to assess topical bioavailability, involve determination of how much of an applied drug actually penetrates skin and how fast (3,4). A wide variety of experimental approaches has been developed, therefore, to answer these questions. However, it must be stated at the outset that (a) there is continuing debate about the factors that influence percutaneous absorption (27–38), and (b) there is as yet no single, generally accepted technique for percutaneous absorption determination, and as a result, there are conflicting opinions concerning the rationale by which an experimental model is selected. The primary division of the methods available is in vivo versus in vitro. The former category involves the use of living skin of humans or experimental animals in situ. The latter employs an isolated skin (or artificial) membrane mounted in a simple diffusion cell. In discussing topical bioavailability from this standpoint, we consider the advantages and disadvantages of these two approaches and indicate their limitations and weaknesses with respect to the objec-