DRUGS AND THE PHARMACEUTICAL SCIENCES VOLUME 18

Dermatological Formulations

Percutaneous Absorption

Brian W. Barry

DERMATOLOGICAL FORMULATIONS

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DERMATOLOGICAL FORMULATIONS

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To Betty and Simon

PREFACE

The theme of this book is how the physicochemical properties of a drug combined into a dosage form affect the percutaneous absorption of the drug after we apply the combination to the skin of a man or an animal. In this context it is necessary to appreciate that for topical therapy, as for other routes of administration, the dosage form of the drug acts as a delivery system. As a consequence any change in the system (either through formulation alterations or through interactions with the organism or the environment) may alter the delivery rate of the drug to the receptor site, together with the total amount of medicament transported to the locus of its action. In dermatological therapy we may refer to the bioavailability of a topical drug as the relative absorption efficiency for the agent. This bioavailability is determined by the release of the drug from the formulation (ointment, cream, lotion, etc.) followed by its penetration through the dead stratum corneum into the viable epidermis and dermis, where the molecule usually produces its characteristic pharmacological response. The ultimate aim in dermatological biopharmaceutics is to design active drug molecules (or prodrugs) with selective permeability, to be incorporated into vehicles which ensure that the medicament arrives at the active site in the biophase at a controlled rate. At the receptor, the drug should maintain a sufficient concentration for the required time.

This book developed from the author's interest in dermatological formulations, and the approach used is a discussion of the fundamental principles of percutaneous absorption rather than specific examples. Many papers in the scientific literature on percutaneous absorption represent a complex blend of physicochemical theory and physiological practicalities. The reader must integrate in his or her mind these two main streams so as to assess the worth of the conclusions. Before this amalgamation can be produced, the reader needs to appreciate the subtleties of the biological and the physicochemical approaches; this book will provide the groundwork for this endeavor.

Chapter 1 introduces the reader to the structure, function, and diseases of human skin and the text provides a brief condensed review of common topical medicaments. A discussion of the basic principles of diffusion through membranes leads on to considerations of skin transport, the routes by which drugs penetrate through the skin, and the role of the epidermal reservoir. Chapter 4 deals with the whole complex of factors that influence percutaneous absorption, classified on the basis of biological or physicochemical considerations. A review of the methods by which we determine the permeation of drugs through skin precedes a discussion on the formulation of dermatological vehicles. The final chapter is rather specialized, as it deals with the flow properties of topical bases; the information presented is directed mainly toward quality control and research and development scientists in the pharmaceutical and cosmetic industries.

The text does not consider specifically the pharmacokinetics of topical therapy or the pharmacodynamics of drug interactions at receptor sites. Pharmacological textbooks and monographs, including Volume 1 and Volume 7 (Chapter 3) in this series, "Drugs and the Pharmaceutical Sciences," present information on these important topics.

The modern trend for scientific books is for an expert to write each chapter so as to provide comprehensive, authoritative treatments. As for other extensive areas of science, it is impossible for any one person to possess a detailed knowledge of all aspects of topical therapy. In contrast, this book is a single-authored text and I trust that the continuity of treatment obtained through an individual aim will compensate for a lack of expertise in specific detail and an inevitable concentration on areas of personal interest.

It is hoped that the book will be useful to pharmacy students and to pharmacists, whether employed in hospital, industry, or community practice, with regulatory authorities, or in teaching and research institutions. Much of the information is also relevant to cosmetic and veterinary scientists and to investigative dermatologists. In particular, the text aims to present a general introduction to the complex subject of percutaneous absorption for those scientists involved in developing topical formulations.

I would like to express my appreciation to Mrs. Marion Firth for her excellent typing, her assistance with the proofreading, and her profound patience in dealing with the many changes made during the preparation of the manuscript. My thanks are also due to Mr. Christopher Bowers and the staff of the Graphic Unit for drawing the diagrams and Mr. J. Merrick and his staff in the Photographic and Film Unit at Bradford University for their help.

Brian W. Barry

DERMATOLOGICAL FORMULATIONS

CONTENTS

— 1 —

STRUCTURE, FUNCTION, DISEASES, AND TOPICAL TREATMENT OF HUMAN SKIN

I. INTRODUCTION

The skin, the heaviest single organ of the body, combines with the mucosal linings of the respiratory, digestive, and urogenital tracts to form a capsule which separates the internal body structures from the external environment. This flexible, self-repairing shell defends the stable internal milieu of living tissues, bathed in their body fluids, from a hostile external world of varying temperature, humidity, radiation, and pollution. The integument not only physically protects the internal organs and limits the passage of substances into and out of the body but also stabilizes temperature and blood pressure with its circulation and evaporation systems. The skin mediates the sensations of touch, pain, heat, and cold; it expresses the redness of anger and embarrassment, the sweating of anxiety, and the pallor of fear; and the integument identifies individuals through the characteristics of the hair, odor, texture, and color shades particular to man.

We may combine these many roles into two purposes: communication between the inside and the outside environments, and control of the former. Now the study of communication and control forms the science of cybernetics (Weiner, 1948), which is therefore an appropriate technology for examining the skin. Mier and Cotton (1976) have reviewed cybernetic concepts in dermatology with particular emphasis on the biochemistry of skin cells.

In the light of the many requirements which the skin must fulfill, it is not surprising that anatomists find that the integument is a very unhomogeneous organ. For an average 70-kg human with a skin surface area of 1.8 m^2, a typical square centimeter covers 10 hair follicles, 12 nerves, 15 sebaceous glands, 100 sweat glands, 3 blood vessels with 92 cm total length, 360 cm of nerves and 3×10^6 cells (Lubowe, 1963; Wells and Lubowe, 1964).

Because the skin is the most accessible tissue of the body, we easily damage it, mechanically, chemically, biologically, and by radiation. Thus, we cut, bruise, and burn it. We often expose the tissue to organic solvents, detergents, chemical residues, and pollutants and to contact allergens produced by bacteria, yeasts, molds, fungi, and plants. Insects and animals sting and bite it. Toiletries, cosmetics, topical and systemic drugs, together with a myriad of skin diseases, may all harm the skin.

In order that we may appreciate and may control the biopharmaceutics of dermatological formulations, and so that we can answer questions regarding the therapeutic and cosmetic properties of the many topical preparations available in the market or on prescription, we need first to understand the skin. We require at least a knowledge of the basic principles of skin anatomy, physiological function, and chemical composition. We also want to know how common diseases and damage alter the skin's properties, in particular its selective barrier function. In general, it is not essential for the formulator to appreciate all the biochemical and molecular subtleties of skin derangements. This chapter presents a simple introduction to the skin, together with a scheme by which we may approach the science of topical formulation, with a simple listing of those topical agents which we commonly employ in dermatology.

II. ANATOMY AND PHYSIOLOGY

The human skin comprises two distinct but mutually dependent tissues, the stratified, avascular, cellular epidermis and an underlying dermis of connective tissue. At the bottom of the dermis lies the fatty, subcutaneous layer (Fig. 1.1). In transverse section, the dermoepidermal junction undulates because a series of thickened epidermal ridges (the rete ridges) project downwards into the dermis. The ridges inscribe characteristic patterns in different regions of the body (Szabo, 1967), which we see best in split skin preparations (Montagna and Parakkal, 1974).

Human skin displays two main types. Hairy skin encloses hair follicles and sebaceous glands, but there are no encapsulated sense organs. Glabrous skin of the palms and the soles constructs a thick epidermis with a compact stratum corneum, but the integument lacks hair follicles and sebaceous glands and the dermis supports encapsulated sense organs. Ridges groove hairless skin into individually unique configurations termed dermatoglyphics. Besides providing identification, for example, fingerprints, dermatoglyphics may aid diagnosis or they may indicate that a patient has an increased tendency to develop certain diseases, for example, alopecia areata or psoriasis (Cummins and Midlo, 1961; Cummins, 1964; Holt, 1968; Verbov, 1968, 1970).

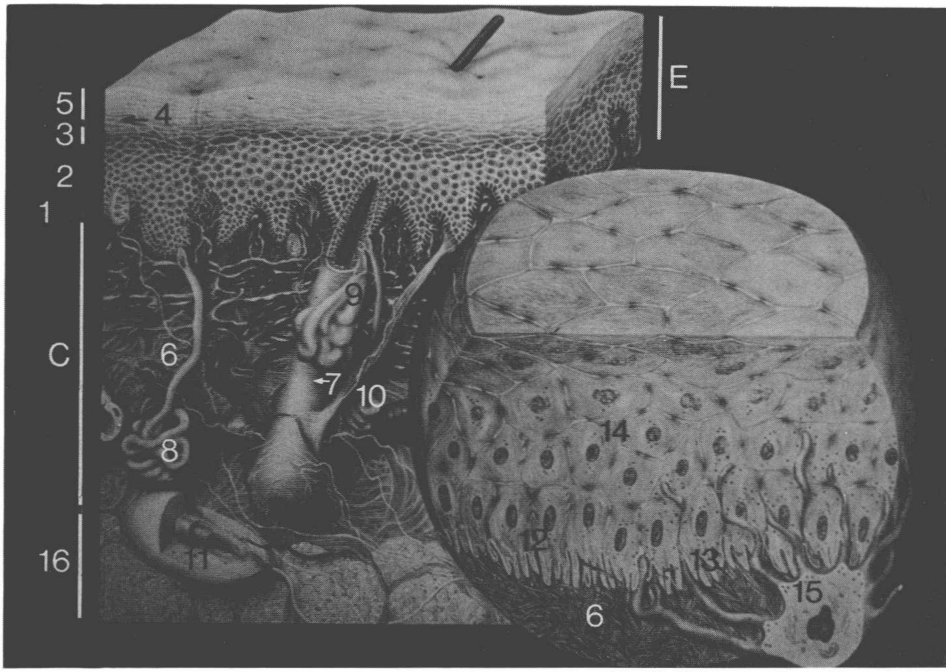

FIG. 1.1 The complex nature of human skin. The inset sphere shows in greater detail the differentiation, development, and keratinization of cells. Key: (E) Epidermis—(1) stratum basale; (2) stratum spongiosum; (3) str-tum granulosum; (4) stratum lucidum; (5) stratum corneum. (C) Corium—(6) collagen fibers; (7) hair roots; (8) sweat glands; (9) sebaceous glands; (10) apocrine glands; (11) Pacini corpuscles; (12) basal membrane; (13) cylindrical basal cells with rete pegs; (14) keratinocytes attached by desmosomes; (15) melanocyte exposed from basal membrane; (16) fat cells. (Reproduced with the kind permission of I.C.I. Pharmaceuticals Ltd.)

A. The Epidermis

The multilayered envelope of the epidermis varies in thickness, depending on cell size and the number of cell layers, ranging from about 0.8 mm on the palms and the soles down to 0.06 mm on the eyelids. Cells which provide epithelial tissue differ from those of all other organs in that as they ascend from the proliferative layer of basal cells they change in an ordered fashion from metabolically active and dividing cells to dense, dead, keratinized protein. We can trace this crucial process if we consider the individual layers in the order in which they form.

1. The basal layer (stratum germinativum) and the dermoepidermal junction

The basal cells are nucleated, columnar, and about 6 μm wide, with their long axis at right angles to the dermoepidermal junction; they connect by cytoplasmic intercellular bridges.

Mitosis of the basal cells constantly renews the epidermis and this proliferation in healthy skin balances the loss of dead horny cells from the skin surface. The epidermis thus remains constant in thickness. Although there are difficulties in calculating epidermal turnover times (Halprin, 1972), workers use tritiated thymadine to selectively label nuclear DNA and thereby they estimate that a cell from the basal layer takes at least 14 days to reach the stratum corneum. In the rapidly proliferating epidermis of psoriasis, the transit time is only 2 days (Epstein and Maibach, 1965; Weinstein and Van Scott, 1965). Radioactive glycine studies indicate that the normal turnover time in the stratum corneum is some 13 or 14 days, with the residence time in psoriatic stratum corneum shortening to 2 days (Rothberg et al., 1961). Therefore, the total turnover times, from the basal layer to shedding, average 28 days in healthy skin and only 4 days in psoriatic skin. The mitotic rate also increases within 24 to 36 hr of injuries such as radiation damage or removal of the stratum corneum by adhesive tape stripping, scrapings, and incisions (Pinkus, 1951, 1952; Weinstein and Frost, 1971). Jarrett (1973) has reviewed epidermal kinetics, and Potten (1975) has estimated the minimal transit time for four regions of the epidermis in mice.

The basal cell layer also includes melanocytes, which produce and distribute melanin granules to the keratinocytes in a complex interaction. The skin requires melanin for pigmentation, a protective measure against radiation (see Sec. III.B.3). Melanocytes lose their activity in vitiligo and hyperactive melanocytes produce tanning, chloasma, freckles, moles, and malignant melanomas (Riley, 1974). Although the melanocyte is the best studied of mammalian cells after the erythrocyte (Fitzpatrick, 1965), for our purposes we need not consider it further here.

Below the basal cell layer lies the complex dermoepidermal junction, which constitutes an anatomic functional unit (Briggaman and Wheeler, 1975). In electron micrographs, the junction spans four components: (1) the basal cell plasma membrane with its specialized attachment devices, the hemidesmosomes; (2) the lamina lucida; (3) the basal lamina; and (4) the fibrous components below the basal lamina, which include anchoring fibrils, dermal microfibril bundles, and collagen fibrils. The "basement membrane" revealed by light microscopy corresponds to the fibrous zone below the basal lamina.

The junction serves the three functions of dermal-epidermal adherence, mechanical support for the epidermis, and control of the passage of cells and some large molecules across the junction. Thus, diseases which operate at this level can markedly reduce the adhesion of the epidermis to the dermis (Briggaman and Wheeler, 1973; Pearson et al., 1974), as can some experimental techniques (Kahl and Pearson, 1967; Briggaman et al., 1971; Jensen and Moffet, 1970). Investigators who use suction to produce blisters in the lamina lucida conclude that the major stabilizing force at the dermo-epidermal junction is a highly viscous bond (Küstala and Mustakallio, 1967; Lowe and Van der Leun, 1968; Peachy, 1971a, b; Hunter et al., 1974; Van der Leun et al., 1974).

We can best consider the barrier function of the junction in terms of three species—small molecules, large molecules, and cells. There is no evidence that the junction significantly inhibits the passage of water, electrolytes, and other low-molecular-weight materials. To do so would, of course, lead to serious consequences with respect to the supply of nutritional materials to the epidermis via the dermal blood vessels. Large molecules also cross the junction [e.g., horseradish peroxidase, a water-soluble protein of molecular weight 40,000 (Schreiner and Wolff, 1969; Squier, 1973) and ruthenium red (Hashimoto and Lever, 1970)]. However, an even larger substance such as thorotrast mainly stays beneath the basal lamina (Wolff and Honigsmann, 1971). It is well established that dermal cellular elements traverse the junction in normal skin and that passage is pronounced in some pathological conditions (Wolff, 1973). The sequence of events is that an area of basal lamina disintegrates, a gap forms in the junction between adjacent cells, and the invading cell penetrates. Finally, basal cells on either side close the gap.

2. The prickle cell layer: the keratinocytes (stratum germinativum)

As the cells produced by the basal layer move outward, they alter morphologically and histochemically. The cells flatten and their nuclei shrink. We call these polygonal cells prickle cells because they interconnect by fine prickles. Each prickle encloses an extension of the cytoplasm, and the opposing tips of the prickles of adjacent cells adhere to form intercellular bridges—the desmosomes. These links maintain the integrity of the epidermis. Between the desmosomes, a capillary space full of tissue fluid separates neighboring cells and the void permits nutrients and oxygen to pass outward. The desmosomes can break and reform to allow migrating melanocytes and leukocytes to pass (De Vargos Lindres and Burgos, 1964).

In spongiosis of early eczema, the intercellular spaces swell with tissue fluid (intercellular edema) but the desmosomes mainly remain intact. With increasing severity of the disease, the desmosomes disrupt and larger spaces (vesicles) form in the epidermis; the process often involves the death and autolysis or premature keratinization of cells. Acantholysis is the separation of individual cells by fracture of desmosomal linkages; this cleavage is a feature of the pemphigus group of blistering diseases.