TOPICAL AND TRANSDERMAL DRUG DELIVERY

Principles and Practice

Edited by
HEATHER A. E. BENSON
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WILEY

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For my husband Tony for his patience and support, and Tom, Sam, and Victoria for their inspiration.

Heather

For my wife Becky, my mum and dad, and my brother Tom.

Adam

Preface

The premise for this book was to provide a single volume covering the principles of transdermal and topical drug delivery and how these are put into practice during the development of new products. We have divided the book into two sections to deal with each of these perspectives and hope that their contents will appeal equally to readers based in academia and industry. We also hope that it will help each of these readers better understand the perspective of the other and therefore aid communication between them.

The first section of the book describes the major principles and techniques involved in the conduct of the many experimental approaches used in the field. We appreciate that these have been covered in previous texts but feel that this section provides a fresh and up-to-date look at these important areas to provide a fundamental understanding of the underlying science in the field. The authors have aimed to provide both the science and practical application based on their extensive experience. The second section of the book provides an insight into product development with an emphasis on practical knowledge from people who work in and with the industry. Designing a new product is about taking different development challenges and decisions into account and always understanding how they may impact the process as a whole. An understanding of the complete process is therefore a prerequisite to maximizing the quality of the product it produces.

As with any such book, we are heavily indebted to our contributors who have all worked hard to produce a text that we believe will be of interest to a cross-section of professionals involved in topical and transdermal product development.

HEATHER A.E. BENSON
ADAM C. WATKINSON

About the Editors

Heather A.E. Benson has extensive experience in drug delivery with particular focus in transdermal and topical delivery. She is an Associate Professor at Curtin University, Perth, Australia, where she leads the Drug Delivery Research Group. In addition she is a director in Algometron Ltd., a Perth-based company involved in the development of a novel pain diagnostic technology, which she co-invented. This technology received the Western Australian Inventor of the Year (Early Stage Category) award in 2008. She is also a scientific advisor to OBJ Ltd., a Perth-based company involved in the development of magnetically enhanced transdermal delivery technologies. Prior to Perth Dr. Benson was at the University of Manitoba, Canada, where she won Canadian Foundation for Innovation funds to establish the Transdermal Research Facility. Before this 2-year period in Canada, she was a senior lecturer at the University of Queensland, Australia, where she worked closely with Professor Michael Roberts to establish a highly successful topical and transdermal research group at the university. Heather has a PhD from Queen's University in Belfast in the area of transdermal delivery and a BSc (Hons) in Pharmacy from Queen's University. She has published extensively on her research and holds a number of patents related to transdermal delivery. She has supervised numerous Masters and PhD students in drug delivery research areas, many of whom now have successful careers in R&D in industry. She is on the editorial board *of Current Drug Delivery* and acts as a reviewer for many journals. She is a member of the CRS Australian Chapter Executive Committee and the Australian Peptide Society Conference Organising Committee.

Adam C. Watkinson has a wealth of experience in the area of drug delivery in general, and transdermal and topical delivery in particular. Until May 2011 he was Chief Scientific Officer at Acrux Ltd. in Melbourne, Australia, where his responsibilities included the strategic leadership of product development, provision of technical support to commercial partnering activities, and regulatory affairs. During his 6 years with Acrux he was a key member of the senior management team and played a pivotal role in the development and approval of Axiron™, a novel transdermal testosterone product that was subsequently licensed to and launched by Eli Lilly in the United States. Prior to Acrux he worked at ProStrakan in Scotland as a Project Manager and Drug Delivery Research Manager. While at ProStrakan he initiated and managed the early development of Sancuso™, the first transdermal granisetron patch that was launched by ProStrakan in the United States in 2008. Before his 5-year stint at ProStrakan, Adam played key roles at An-eX in Wales, a company that provides R&D development services in the area of percutaneous absorption to

the pharmaceutical, cosmetic, and agrochemical industries. Adam has an MBA from Cardiff University, a PhD from the Welsh School of Pharmacy in the area of transdermal delivery, and a BSc in Chemistry from the University of Bath. He has published extensively on his research, is the author of several patents, and holds an Honorary Chair at the School of Pharmacy at the University of London. He is also an Associate Lecturer at Monash University in Melbourne, Australia, and has long been a member of the Scientific Advisory Board for the international PPP (Perspectives on Percutaneous Penetration) conference. Despite his lengthy allegiance to industry he has co-supervised several PhD students and is an advocate of encouraging students to interact with industry as early and as much as possible. Having recently returned from Australia he has set up a U.K.-based consultancy firm (Storith Consulting Limited in Kent) offering advice in the areas of drug development and topical and transdermal drug delivery.

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Contents

Part One

Current Science, Skin Permeation, and Enhancement Approaches

Chapter 1

Skin Structure, Function, and Permeation

Heather A.E. Benson

INTRODUCTION

The skin is the largest organ of the body, covering about 1.7 m^2 and comprising approximately 10% of the total body mass of an average person. The primary function of the skin is to provide a barrier between the body and the external environment. This barrier protects against the permeation of ultraviolet (UV) radiation, chemicals, allergens and microorganisms, and the loss of moisture and body nutrients. In addition, the skin has a role in homeostasis, regulating body temperature and blood pressure. The skin also functions as an important sensory organ in touch with the environment, sensing stimulation in the form of temperature, pressure, and pain.

While the skin provides an ideal site for administration of therapeutic compounds for local and systemic effects, it presents a formidable barrier to the permeation of most compounds. The mechanisms by which compounds permeate the skin are discussed later in this chapter, and methods to enhance permeation are described in Chapters 2–4. An understanding of the structure and function of human skin is fundamental to the design of optimal topical and transdermal dosage forms. The structure and function of healthy human skin is the main focus of this chapter. Physiological factors that can compromise the skin barrier function, including age-related changes and skin disease, are also reviewed. Chapter 19 describes the current and future trends in the treatment of these and other skin diseases.

HEALTHY HUMAN SKIN: STRUCTURE AND FUNCTION

Human skin is composed of four main regions: the stratum corneum, the viable epidermis, dermis, and subcutaneous tissues (Fig. 1.1). A number of appendages are

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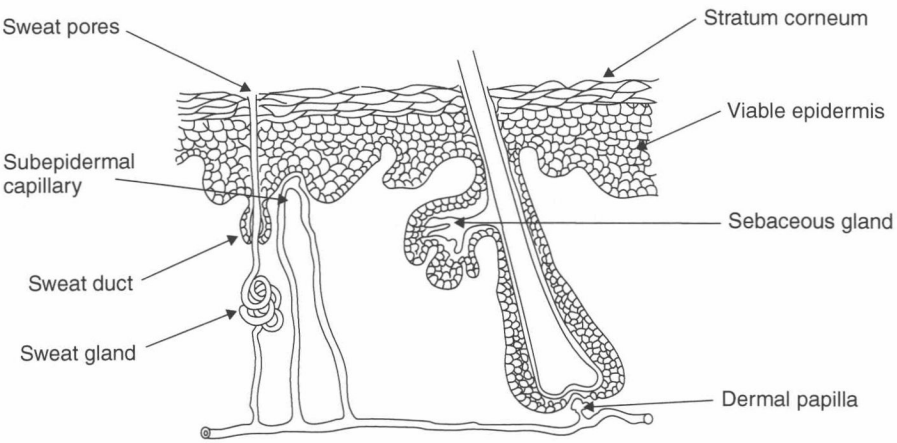

Figure 1.1 Diagrammatic cross-section of human skin.[96]

associated with the skin: hair follicles and eccrine and apocrine sweat glands. From a skin permeation viewpoint, the stratum corneum provides the main barrier and therefore the structure of this layer will be discussed in most detail. The other layers and appendages contribute important functions and are important target sites for drug delivery.

Epidermis

The epidermis is a multilayered region that varies in thickness from about 0.06 mm on the eyelids to about 0.8 mm on the palms of the hands and soles of the feet. There are no blood vessels in the epidermis, therefore epidermal cells must source nutrients and remove waste by diffusion across the epidermal–dermal layer to the cutaneous circulation in the dermis. Consequently, cells loose viability with increasing distance from the basal layer of the epidermis. The term "viable epidermis" is often used for the epidermal layers below the stratum corneum, but this terminology is questionable, particularly for cells in the outer layers. The epidermis is in a constant state of renewal, with the formation of a new cell layer of keratinocytes at the stratum basale, and the loss of their nucleus and other organelles to form desiccated, proteinaceous corneocytes on their journey toward desquamation, which in normal skin occurs from the skin surface at the same rate as formation. Thus the structure of the epidermal cells changes from the stratum basale, through the stratum spinosum, stratum granulosum, and stratum lucidum to the outermost stratum corneum (Fig. 1.2). The skin possesses many enzymes capable of metabolizing topically applied compounds. These are involved in the keratinocyte maturation and desquamation process,[1] formation of natural moisturizing factor (NMF) and general homeostasis.[2]

While the stratum corneum provides an efficient physical barrier, when damaged, environmental contaminants can access the epidermis to initiate an immunological response. This includes (1) epithelial defense as characterized by antimicrobial

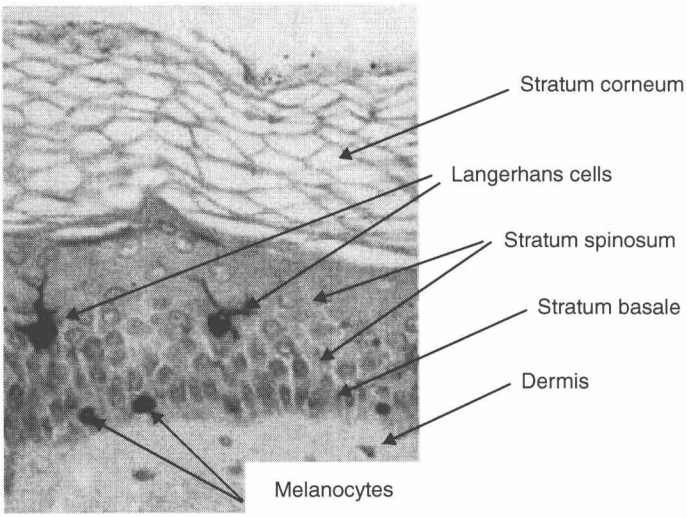

Figure 1.2 Human epidermis.[97]

peptides (AMP) produced by keratinocytes—both constitutively expressed (e.g., human beta defensin 1 [hBD1], RNAse 7, and psoriasin) and inducible (e.g., hBD 2-4 and LL-37); (2) innate-inflammatory immunity, involving expression of pro-inflammatory cytokines and interferons; and (3) adaptive immunity based on antigen presenting cells, such as epidermal Langerhans and dendritic cells, mediating a T cell response.[3] An understanding of these systems is important as they can be involved in skin disease and may also be therapeutic targets for the management of skin disease. The importance of these systems as therapeutic targets is highlighted in Chapter 19.

Stratum Basale

The stratum basale is also referred to as the stratum germinativum or basal layer. This layer contains Langerhans cells, melanocytes, Merkel cells, and the only cells within the epidermis that undergo cell division, namely keratinocytes. The keratinocytes of the basal lamina are attached to the basement membrane by hemidesmosomes, which are proteinaceous anchors.[4,5] The absence of this effective adhesion results in rare chronic blistering diseases such as pemphigus and epidermolysis bullosa. Within the epidermis, desmosomes act as molecular rivets, interconnecting the keratin of adjacent cells, thereby ensuring the structural integrity of the skin.

Langerhans cells are dendritic cells and the major antigen presenting cells in the skin. They are generated in the bone marrow, and migrate to and localize in the stratum basale region of the epidermis. When activated by the binding of antigen to the cell surface, they migrate from the epidermis to the dermis and on to the regional lymph nodes, where they sensitize T cells to generate an immune response.