
Percutaneous Penetration Enhancers

Chemical Methods in Penetration Enhancement

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Howard I. Maibach
Editors

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Drug Manipulation Strategies
and Vehicle Effects

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ISBN 978-3-662-45012-3 ISBN 978-3-662-45013-0 (eBook)
DOI 10.1007/978-3-662-45013-0

Library of Congress Control Number: 2014958975

Springer Berlin Heidelberg New York Dordrecht London

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Printed on acid-free paper

Springer-Verlag GmbH Berlin Heidelberg is part of Springer Science+Business Media
(www.springer.com)

Preface

The main function of skin is the protection of the body from the external environment by preventing loss of water and the ingress of exogenous substances. This implies that the skin acts as a barrier for the diffusion of substances into the underlying tissue. Despite this role, the skin has become recognized as an important drug delivery route which can be reached directly. It is an ideal site for the application of drugs for achieving local (topical) and systemic (transdermal) drug effects. Local or topical drug delivery assumes treating various skin diseases, while transdermal delivery aims to achieve systemically active drug levels in order to treat systemic diseases. Drugs have been applied to the skin to achieve also regional drug delivery which involves drug application to the skin to treat or alleviate disease symptoms in deep tissues beneath the skin (such as in musculature, etc.). Topical and transdermal drug delivery offer a number of advantages compared to other conventional routes, and hence they are of great interest to pharmaceutical research, which explains the increasing interest in skin as a site of drug application.

However, skin represents a formidable barrier for percutaneous drug absorption, being of crucial importance for achieving topical and transdermal effects of drugs. Significant efforts have been devoted to developing strategies to overcome the impermeability of intact human skin. There are many ways for circumventing the stratum corneum, which provides the main barrier to drug penetration. These methods can be divided into chemical and physical penetration enhancement methods, i.e. percutaneous penetration enhancers, which are described in this book series *Percutaneous Penetration Enhancers*.

The aim of this book series is to provide to readers working in academia and industry, including young researchers, an up-to-date comprehensive work describing all the important topics required to understand the principles of enhancing transdermal and dermal drug delivery. The book series contains five books.

The book *Chemical Methods in Penetration Enhancement: Drug Manipulation Strategies and Vehicle Effects* begins with a description of the skin, as understanding of its structure, function and especially its penetration pathways is fundamental to understanding how topical and transdermal dosage forms work and how different methods may be employed to enhance percutaneous drug penetration. The first two parts of the book devoted to skin and the stratum corneum, representing its uppermost layer being responsible for its protection, discuss their structure, the importance of the lipid organization in the stratum corneum, the different penetration pathways through the skin

with an emphasis on the increasing importance of the follicular route, as well as the influence of different excipients on the skin. The focus of the book is on the chemical methods used to overcome the impermeability of intact skin, such as different drug manipulation strategies (drug or prodrug selection, chemical potential control, eutectic systems, complexes with cyclodextrines, etc.) and formulation/vehicle effects (influences of: emulsions, nanoemulsions, pickering emulsions, microemulsions, emulsifiers, emollients, liquid crystalline structures, gels, etc.) on the penetration enhancement of drugs.

The book *Chemical Methods in Penetration Enhancement: Nanocarriers* describes similarly to the first book chemical methods used in penetration enhancement of drugs. However, this book is devoted to the application of different kinds of nanocarriers and represents an attempt to familiarize the readers with the importance of nanocarriers used to enhance the percutaneous penetration of drugs as they have numerous advantages in comparison to conventional drug formulations. More recently, different types of nanocarriers have been designed by researchers which allow controlled and targeted drug delivery (dermal or transdermal drug delivery), improved therapeutic effectiveness and reduced side effects of drugs. As carriers they can be classified into lipid-based vesicles (e.g. liposomes, transfersomes, invasomes, etc.), surfactant-based vesicles (e.g. niosomes, novasomes and others), lipid-based particulate carriers (e.g. solid lipid nanoparticles, nanostructured lipid carriers and lipid nanocapsules), polymer-based particulate carriers (e.g. polymeric nano- and microparticles, polymeric nanocapsules, polymeric micelles, dendrimers, dendritic core-multishell nanocarriers, etc.), nanocrystals and others. This book focusing on the different nanocarriers gives a comprehensive review of their use as promising dermal and transdermal drug delivery systems. It also considers the use of nanocarriers for cutaneous immunization offering the important advantage of being painless and having a stronger immune response compared to the intramuscular injection of vaccines. In addition, the book provides insights on the safety of the use of nanoparticles.

The book *Chemical Methods in Penetration Enhancement: Modification of the Stratum Corneum* similarly to the aforementioned two books describes the chemical methods used in penetration enhancement of drugs with an emphasis on the enhancing methods used to modify the stratum corneum. It starts with the classification of penetration enhancers, their mode of action and provides insights on the structure–activity relationship of chemical penetration enhancers. The focus of this book is on the most commonly used classes of skin penetration enhancers being investigated in scientific literature and used in commercial topical and transdermal formulations, and their representatives are discussed in more detail, including their mechanism of action, where known. The following penetration enhancers are considered in the book: alcohols (e.g. ethanol, etc.), glycols (e.g. propylene glycol, etc.), amides (e.g. 1-dodecylazacycloheptan-2-one or laurocapram (Azone®), etc.), fatty acids (e.g. oleic acid, etc.), fatty acid esters (e.g. isopropyl myristate, etc.), ether alcohols (e.g. diethylene glycol monoethyl ether (Transcutol®)), pyrrolidones (e.g. N-methyl-2-pyrrolidone, etc.), sulphoxides (e.g. dimethyl sulphoxide, etc.), surfactants (e.g. polysorbates, etc.), terpenes (e.g. L-menthol, etc.), peptides and new classes of enhancers, such as iminosulfuranes,

transcarbams, dimethylamino acid esters and dicarboxylic acid esters. In addition, synergistic effects of different chemical penetration enhancers have been discussed in the book as an important feature of chemical penetration enhancers. Furthermore, the safety profile of chemical penetration enhancers is considered.

The book *Physical Methods in Penetration Enhancement* considers the current status and possible future directions in the emerging area of physical methods being used as potent enhancers for the percutaneous penetration of drugs. It gives a comprehensive overview of the most used methods for enhancing dermal and transdermal drug delivery. It covers sonophoresis, iontophoresis, electroporation, magnetophoresis, microneedles, needle-free jet injectors, ablation methods (electrical, thermal or laser skin ablation) and others. The numerous advantages of these methods have opened new frontiers in the penetration enhancement of drugs for dermal and transdermal drug delivery. Cutaneous vaccination and gene delivery by physical methods have been also discussed in this volume. Consideration was given to new methods, too, such as a novel electrochemical device for penetration enhancement, different waves (e.g. photoacoustic waves, microwaves, etc.), natural submicron injectors, moxibustion and others. Furthermore, the combined use of different physical methods or of physical methods and passive enhancement methods (chemical penetration enhancement methods) are discussed as they provide, due to their synergistic effects, higher percutaneous drug penetration when used together.

The book *Drug Penetration Into/Through the Skin: Methodology and General Considerations* provides fundamental principles of the drug penetration into/through the skin, from covering basic mathematics involved in skin permeation of drugs, influences of drug application conditions and other factors on drug penetration, mechanistic studies of penetration enhancers, influences of the type of skin used (human native or reconstructed skin) to different methods utilized to assess the drug penetration into/through the skin and to determine the amount of permeated drug (such as tape stripping of the stratum corneum, electron spin resonance, Raman spectroscopy, attenuated total reflection, confocal laser scanning microscopy, single and multiphoton microscopy, etc.). Retardation strategies are also discussed as being important for some classes of substances, such as sunscreens. The safety of applied penetration enhancers as well as the research ethics in the investigation of dermal and transdermal drug delivery are addressed in this book. The book ends with the current status and future perspectives of passive/chemical and active/physical penetration enhancement methods as they are gaining extensive interest as promising tools to enable an efficient dermal or transdermal drug delivery.

We are very thankful to all the authors who contributed chapters to the book series *Percutaneous Penetration Enhancers*, as they found time to work on the chapters despite having busy schedules and commitments. All the authors are eminent experts in the scientific field which was the subject of their chapter, and hence their contribution raised the value of the book. We also sincerely thank our collaborators from Springer: Ellen Blasig, Isabella Formento, Sverre Klemp, Srinath Raju, Andre Tournois, Grant Weston and

Portia Formento Wong, for their dedicated work which was necessary to achieve such a high standard of publication. We highly appreciate readers' comments, suggestions and criticisms to improve the next edition of the book series.

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