

Preface

Academia and industry have expressed a high interest throughout the past three decades in delivering drugs to or across the oral mucosa for the purpose of achieving desired therapeutic outcomes. However, because the membranes that line the oral cavity exhibit relatively poor permeability to drugs, and due to the fact that only a limited number of drugs possess the innate physicochemical properties to allow them to inherently cross the mucosa in clinically relevant amounts, we have failed to witness a large number of oral mucosal drug delivery systems become commercially available. This situation has stimulated much interest in conducting research that has focused on increasing the potential drug candidate list for oral mucosal therapeutic applications. Research on the use of oral mucosal permeation enhancers and mucoadhesives has resulted in advances in our knowledge of how to modify drug permeation through the oral mucosa and delivery system retention at the site of administration.

It is the editors' belief that the prospect of the oral cavity as a site for drug delivery has yet to meet its full potential and that the oral mucosal route of administration is ideally suited to improve the delivery of several existing drugs. Such delivery systems would offer market differentiation for these drugs through improved, pain-free, patient-friendly delivery systems that, when optimized, would offer a definite therapeutic improvement over existing treatments. However, great challenges face formulators who aim to deliver drugs locally to the membranes that line the oral cavity or systemically across the oral mucosa. Such challenges require innovative solutions to create drug delivery systems that provide a convenient, patient-acceptable means to relieve clinical symptoms and include ingredients that manipulate the bioavailability of drugs across the oral mucosa or provide prolonged retention at the site of absorption. This volume examines the area of oral mucosal drug delivery and the therapeutic opportunities for the use of the oral mucosa as a site of administration for drug delivery. It is our hope that the contents of this book will arm future researchers with the relevant information for them to develop new drug delivery systems that result in the oral mucosa becoming an important future site of administration for drug delivery.

In Chap. 1, Thomas P. Johnston reviews the most relevant aspects of oral mucosal and mouth anatomy and physiology and relates its relevance to local and

systemic oral transmucosal drug delivery. Some of the concepts addressed involve the advantages and disadvantages of oral mucosal drug delivery, the various sites of drug delivery within the mouth, factors that influence drug delivery associated with the gross and the microenvironment within the oral cavity (e.g., mucus, saliva, and salivary glands), and practical considerations regarding tissue irritation and/or damage when using this route of drug administration. Johnston also examines the role of permeation enhancers and buffering agents/pH modifiers in oral transmucosal drug delivery. The fundamental anatomical and physiological information provided in this chapter will build a sound background for those pharmaceutical scientists directly involved with the formulation of dosage forms intended for oral mucosal drug delivery.

In Chap. 2, Rathbone, Pather, and Şenel explore the reasons for developing oral mucosal drug delivery systems, and identify the key considerations in the design and development of oral mucosal drug delivery systems. Throughout the chapter, the authors describe the characteristics of many of the delivery systems that have been successfully developed and commercialized for use in this site for drug delivery.

The permeability of many drugs through the mucosa of the oral cavity is slow due to the inherent barrier properties of the mucosa that line the oral cavity. Therefore, the enhancement of permeation of the drug is needed to extend the drug candidate list for this route of administration. In Chap. 3, Pather and Kolli examine the use of chemicals that promote the passage of the drug through the oral mucosa and describe the different classes of compounds that may be useful to enhance oral mucosal drug permeation. Pather and Kolli adopt a broad view of the concept of “chemical methods for enhancing delivery,” thus, effervescent agents and chemicals that assist in retaining the dosage form on the mucosa for an extended time, thereby allowing a longer time for drug permeation, are included in this chapter.

In Chap. 4, Sandri et al. examine the mechanism of action, functional characteristics, selection, and assessment of mucoadhesive polymers as enabling excipients for oral mucosal drug delivery. The authors identify and discuss several classes of polymers that have been proved to possess pronounced adhesion properties when placed in contact with oral mucosa. They also define the key properties that facilitate these molecules achieving prolonged adhesion onto oral mucosa, which include their ability to spread over the mucosal surface, their swelling properties, their ionic (cationic and anionic) charge density, and their hydration and consequent mucus dehydration properties. The chapter provides an in-depth look at the assessment of the mucoadhesive properties of the compounds and the rationale for their selection by the formulation scientist for their inclusion in an oral mucosal drug delivery system.

Authors Giannola, De Caro, and Sutura examine the physical methods for enhancing oral mucosal delivery in Chap. 5. The authors examine the use of sonophoresis, iontophoresis, and electroporation methods in the area of oral mucosal drug delivery and review the ability of these techniques to increase the drug flux through the oral mucosal membranes. The authors highlight that these physical methods are extensively used to enhance drug permeation through the skin but have yet to become widely used for increasing drug permeation of the membranes that line

the oral cavity, despite the fact that they are very promising in this regard and are gaining in popularity due to their noninvasive and convenient means for local or systemic delivery of drugs.

In Chap. 6, Kolli and Pather define the methods used to characterize oral mucosal drug delivery from the perspective of both the drug and its formulation. The authors highlight that even though drug delivery across the oral mucosa has emerged as a useful alternative for compounds that cannot be delivered orally, standardized methods to evaluate drug absorption across oral mucosal membranes, either *in vitro* or *in vivo*, and standardized techniques used to characterize oral mucosal drug delivery systems have yet to be agreed upon. Their chapter provides a comprehensive review of the current *in vitro* and *in vivo* methodologies employed in the literature for evaluating oral transmucosal absorption of compounds. In addition, it reviews the use of buccal cell cultures as a means to study oral mucosal drug absorption. In the second part of their chapter, the authors examine of the methods used to test oral mucosal drug formulations including residence time, mucoadhesion and drug release.

In Chap. 7, Rathbone, Pather, and Şenel take an in-depth look at systemic controlled release oral mucosal drug delivery systems and the clinical opportunities that currently exist for this type of drug product. The chapter describes the potential of the oral cavity as a site for the systemic delivery of drugs alongside some of the problems and their solutions and examines the research in these areas and how they have resulted in extending the clinical opportunities for the use of the oral mucosa as a site for drug delivery.

Tablets for systemic oral mucosal drug delivery are reviewed in Chap. 8 by Rane and Moe. The chapter focuses on the formulation and performance of solid dosage forms commonly used in oral transmucosal delivery. The authors highlight the specific challenges associated with the oral cavity as a route of drug administration together with the products used for transmucosal delivery that are more effective and sometimes safer than conventional dosage forms. They also discuss clinical studies that directly compare conventional dosage forms with oral transmucosally delivered products. The authors expertly define the basic principles of oral transmucosal drug delivery and explore new developments in-depth. Examples of formulation technologies and clinical performance from successful and widely known oral transmucosally delivered products are provided. Overall, this chapter comes to the conclusion that there is a large scope in further development of strategies for oral transmucosal drug delivery that could be applied to as yet unexplored molecules.

A relatively new area of research and application of the oral cavity is that of the formulation of delivery systems for photosensitisers that are therapeutically used in oral cavity photodynamic therapy. Photodynamic therapy is a clinical treatment that combines the effects of visible light irradiation with subsequent biochemical events that arise from the presence of a photosensitizing drug to cause destruction of selected cells. Following administration, the photosensitizer accumulates in the target cells and a measured light dose of appropriate wavelength is then used to irradiate the target tissue that activates the drug. In Chap. 9, Donnelly reviews the current status and future potential of this area to oral mucosal drug delivery. The

chapter provides a clear message that photodynamic therapy has an important role to play in the treatment of neoplastic and dysplastic disease at body sites amenable to irradiation, and in the future this may include the oral cavity where local delivery can have a large role to play in the treatment of such local oral mucosal diseases.

In Chap. 10, Caramella et al. describe the current status of medical devices as a supportive care for oromucosal pathologies. The chapter examines the opportunities offered by medical devices and provides an interesting example, even though there are currently many unmet needs in the treatment of oromucosal pathologies. The authors introduce the area that includes definitions and relevant regulations and the oral conditions that can be treated with a medical device. In addition, the mechanisms of action by which medical devices function are reviewed, and a list of products available on the market is included in the chapter. At the end of the chapter, the authors summarize their ongoing work in this area and provide a fascinating case study on a new improved class II medical device.

In the final chapter, Hughes and Ghosh provide a general overview of the U.S. Food and Drug Administration's regulatory considerations for intraoral drug product development and marketing approval. The authors highlight that effective drug delivery through the oral mucosa is complex, and only a few products have so far achieved commercial success. They discuss the often unpredictable scientific hurdles and suggest that a good understanding of the regulatory requirements for product development is critical for maximizing resources and positive interactions with the regulatory authorities. The chapter provides an overview that will allow scientists to successfully navigate through the U.S. regulatory approval process and underscores that such an attempt will require an interdisciplinary approach from the legal, clinical, chemistry, clinical pharmacology, nonclinical and biopharmaceutics perspectives.

The editors of this volume sincerely thank the authors for their time, efforts and patience in the compilation of this volume. We are indebted to their exceptional knowledge and understanding of the area and for their willingness to put down in words and share their years of experience in this field. We have enjoyed the opportunity to compile the book, and we hope that other scientists will benefit from reading the authoritative chapters contained within this volume.

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