

# ***Drug Development and Industrial Pharmacy®***

All Dekker journals are online  
[research + dekker.com](http://research + dekker.com) → results

*Drug Regulatory Affairs*

*Formulation Including  
Pharmacokinetic Aspects*

*International Pharmaceutical Issues*

*Good Manufacturing Practice*

*Quality Control*

PHARMACY LIBRARY  
UNIVERSITY OF WISCONSIN

OCT 08 2003

Madison, WI 53705

VOLUME 29 NUMBER 8 2003

Teva Pharm. v. Indivior, IPR2016-00280  
INDIVIOR EX 2011 - 1/15

89079994133



b89079994133a

## DRUG DEVELOPMENT AND INDUSTRIAL PHARMACY®

Volume 29, Number 8, 2003

## CONTENTS

## REVIEW

- Buccal Delivery Systems** ..... 821  
*J. Hao and P. W. S. Heng*

## RESEARCH PAPERS

- Dissolution and Absorption Modeling: Model Expansion to Simulate the Effects of Precipitation, Water Absorption, Longitudinally Changing Intestinal Permeability, and Controlled Release on Drug Absorption** ..... 833  
*K. C. Johnson*
- Acrylic Matrix Type Nicotine Transdermal Patches: In Vitro Evaluations and Batch-to-Batch Uniformity** ..... 843  
*T. Pongjanyakul, S. Prakongpan, and A. Priprem*
- Nimesulide-Modified Gum Karaya Solid Mixtures: Preparation, Characterization, and Formulation Development** ..... 855  
*G. V. Murali Mohan Babu, N. Ravi Kumar, K. Himasankar, A. Seshasayana, and K. V. Ramana Murthy*
- Influence of the Metering Chamber Volume and Actuator Design on the Aerodynamic Particle Size of a Metered Dose Inhaler** ..... 865  
*J. Berry, S. Heimbecher, J. L. Hart, and J. Sequeira*
- Evaluation of the Film-Forming Property of Hydrogenated Rosin** ..... 877  
*P. M. Satturwar, S. V. Fulzele, S. B. Joshi, and A. K. Dorle*
- Effect of Lipid Excipients on In Vitro Pancreatic Lipase Activity** ..... 885  
*R. Subramanian and K. M. Wasan*
- Different Dissolution Media Lead to Different Crystal Structures of Talinolol with Impact on Its Dissolution and Solubility** ..... 891  
*D. Wagner, N. Glube, N. Berntsen, W. Tremel, and P. Langguth*
- Potential Use of Cyclodextrins to Enhance the Solubility of YM466 in Aqueous Solution** ..... 903  
*K. Nakamura, K. Tokihiro, Y. Motomura, S. Nishide, and S. Yokohama*
- The Influence of Polymeric Subcoats and Pellet Formulation on the Release of Chlorpheniramine Maleate from Enteric Coated Pellets** ..... 909  
*L. D. Bruce, J. J. Koleng, and J. W. McGinity*
- Pharmaceutical Applications of Shellac: Moisture-Protective and Taste-Masking Coatings and Extended-Release Matrix Tablets** ..... 925  
*N. Pearnchob, J. Siepmann, and R. Bodmeier*

MARCEL  
DEKKER, INC.

NEW YORK • BASEL

Contributions to this journal are published free of charge

## DRUG DEVELOPMENT AND INDUSTRIAL PHARMACY®

---

**Disclaimer.** The material in this publication is for general information only and is not intended to provide specific advice or recommendations for any individual. This publication is sold with the understanding that the publisher is not engaged in rendering professional services. In such a case where medical or other professional advice is needed, you should consult the appropriate health care or other professional for advice with regard to your individual situation. The publisher disclaims all liability in connection with the use of information contained in this publication.

Contributions to this journal are published free of charge. Effective with Volume 10, Number 4, this journal is printed on acid-free paper.

Copyright © 2003 by Marcel Dekker, Inc. All rights reserved. Neither this work nor any part may be reproduced or transmitted in any form or by any means, electronic or mechanical, microfilming and recording, or by any information storage and retrieval systems without permission in writing from the publisher.

[www.dekker.com](http://www.dekker.com)

REVIEW

## Buccal Delivery Systems

Jinsong Hao and Paul W. S. Heng\*

Department of Pharmacy, National University of Singapore, Singapore

### ABSTRACT

The oral cavity is an attractive site for drug delivery due to ease of administration and avoidance of possible drug degradation in gastrointestinal tract and first-pass metabolism. Buccal drug delivery specifically refers to the delivery of drugs within/through buccal mucosa to affect local/systemic pharmacological actions. This review briefly describes advantages and limitations of buccal drug delivery, anatomical structure of oral mucosa, and methodology in evaluating buccal drug delivery system, focusing on physiology, pharmacology, pathology, and formulation design in line with recent developments in buccal delivery systems.

*Key Words:* Buccal delivery; Bioadhesion; Penetration enhancer; Enzyme inhibitor; Formulation design.

### INTRODUCTION

The oral cavity is an attractive site for drug delivery due to ease of administration and avoidance of possible drug degradation in the gastrointestinal tract and first-pass metabolism. There are four potential regions for drug delivery in the oral cavity, namely buccal, sublingual, palatal, and gingival. Buccal drug delivery specifically refers to the delivery of drugs within/through the buccal mucosa to affect local/systemic pharmacological actions. Buccal-delivered drugs may be used for treatment of diseases in the

oral cavity or for systemic use.<sup>[1]</sup> However, inherent limitations, including short residence time, small absorption area, and barrier property of the buccal mucosa, are challenges to buccal drug delivery.

Oral mucosal and bioadhesive drug delivery systems have been well documented.<sup>[1,2]</sup> This article will briefly describe advantages and limitations of buccal drug delivery, anatomical structure of oral mucosa, and methodology in evaluating buccal drug delivery systems, focusing on physiology, methodology, and formulation design in line with recent developments in buccal delivery systems.

\*Correspondence: Paul W. S. Heng, Department of Pharmacy, National University of Singapore, 18 Science Drive 4, 117543, Singapore; Fax: 65-67752265; E-mail: phapaulh@nus.edu.sg.

## ANATOMY AND BIOCHEMISTRY OF ORAL MUCOSA

Oral mucosa is lined with an epithelium supported by a connective tissue termed lamina propria and separated from the epithelium by a basal membrane. The epithelium of oral mucosa is stratified with regional variation in terms of structure and function.<sup>[1]</sup> Three types of oral mucosa are referred to as masticatory, lining, and specialized mucosa. The epithelium of masticatory mucosa in gingival and hard palate regions is keratinized and further subdivided into four layers, namely, keratinized, granular, prickle-cell, and basal layers. The nonkeratinized epithelium of lining mucosa covers the remaining regions, except the dorsal surface of the tongue and is made up of superficial, intermediate, prickle-cell, and basal layers. Specialized mucosa in the dorsum of the tongue consists of both keratinized and nonkeratinized mucosa. The physiological structure of buccal mucosa is illustrated in Fig. 1. Small vessels and capillaries that open to the internal jugular vein distribute within the lamina propria, thus avoiding the hepatic first-pass clearance of buccal-delivered drugs. Blood flow in the oral mucosa is generally faster and richer than that in the skin.<sup>[1,3]</sup> The nonkeratinized buccal mucosa was reported to have approximately a thickness of 500–600  $\mu\text{m}$  and surface area of 50.2  $\text{cm}^2$ .<sup>[1]</sup>

Membrane-coating granules are small lipid organelles in the prickle-cell layer.<sup>[1]</sup> The intercellular lipids discharged from membrane-coating granules are responsible for the epithelial cohesion and formation of the superficial permeability barrier in the epithelium.<sup>[3]</sup> This main penetration barrier exists in the outermost quarter to one-third of the epithelium. The keratinized epithelia contain more neutral lipids that are associated with the barrier function, while nonkeratinized epithelia contain more polar lipids.<sup>[4]</sup> The loosely packed intercellular

lipids and the presence of large amounts of phospholipids in nonkeratinized, even in keratinized mucosa, account for the overall higher permeability of the oral mucosa than that of the skin stratum corneum.<sup>[5]</sup> The nonkeratinized mucosa is more permeable than the keratinized mucosa, forming the major administration site in the oral cavity. The oral mucosal membranes do not have tight junctions as seen in intestinal membranes.<sup>[1]</sup>

The secretion of saliva from salivary glands features regional, individual, and time variations.<sup>[1]</sup> The buccal region contains minor salivary glands. The mucus layer covers the oral mucosal surface and serves to lubricate and protect as well as to act as a wetting agent. Mucin is a group of glycoproteins composed of oligosaccharide side chains attached to a protein core. Three-quarters of the protein core are heavily glycosylated and impart a gel-like characteristic to mucus. The remaining nonglycosylated groups are involved in cross-linking via disulfide bonds among mucin molecules.<sup>[4]</sup> Mucus is negatively charged at physiological saliva pH of 5.8–7.4 because of the presence of sialic acids ( $\text{pK}_a = 2.6$ ) and ester sulfates at the terminals of some pendant oligosaccharide side chains.<sup>[4]</sup>

## GENERAL CONSIDERATIONS IN FORMULATION DESIGN

### Physiological Aspects

The buccal mucosa has a very limited area for application of the buccal delivery system, thus limiting device size and drug load. The actual area for drug absorption depends on the size of the dosage form. Generally, a device with the size of 1–3  $\text{cm}^2$  and a daily dose of 25 mg or less would be preferred for buccal delivery.<sup>[4,6]</sup> The maximal duration of buccal drug delivery is approximately 4–6 h, as meal

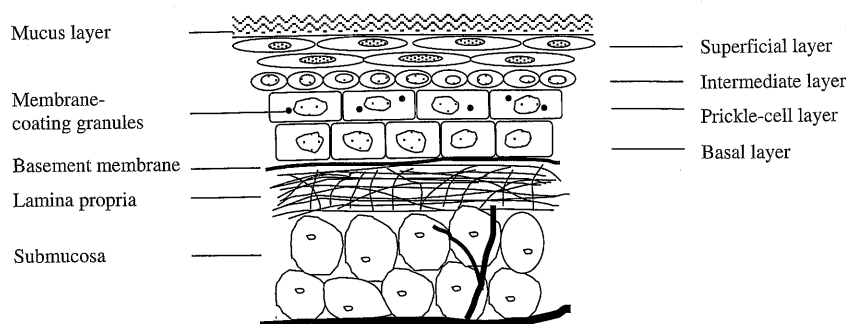


Figure 1. Schematic representation of physiological structure of buccal layer.

# Explore Litigation Insights

Docket Alarm provides insights to develop a more informed litigation strategy and the peace of mind of knowing you're on top of things.

## Real-Time Litigation Alerts



Keep your litigation team up-to-date with **real-time alerts** and advanced team management tools built for the enterprise, all while greatly reducing PACER spend.

Our comprehensive service means we can handle Federal, State, and Administrative courts across the country.

## Advanced Docket Research



With over 230 million records, Docket Alarm's cloud-native docket research platform finds what other services can't. Coverage includes Federal, State, plus PTAB, TTAB, ITC and NLRB decisions, all in one place.

Identify arguments that have been successful in the past with full text, pinpoint searching. Link to case law cited within any court document via Fastcase.

## Analytics At Your Fingertips



Learn what happened the last time a particular judge, opposing counsel or company faced cases similar to yours.

Advanced out-of-the-box PTAB and TTAB analytics are always at your fingertips.

## API

Docket Alarm offers a powerful API (application programming interface) to developers that want to integrate case filings into their apps.

## LAW FIRMS

Build custom dashboards for your attorneys and clients with live data direct from the court.

Automate many repetitive legal tasks like conflict checks, document management, and marketing.

## FINANCIAL INSTITUTIONS

Litigation and bankruptcy checks for companies and debtors.

## E-DISCOVERY AND LEGAL VENDORS

Sync your system to PACER to automate legal marketing.