

European journal of pharmaceuticals and biopharma  
v. 77, no. 2 (Feb. 2011)  
General Collection  
W1 EU72DPK  
2011-03-04 15:27:21

February 2011

ISSN 0939-6411  
77(2) 187-336

ELSEVIER

# European Journal of Pharmaceuticals and Biopharmaceuticals



PROPERTY OF THE  
NATIONAL  
LIBRARY OF  
MEDICINE

Official Journal of



International Association for Pharmaceutical Technology  
Arbeitsgemeinschaft für Pharmazeutische Verfahrenstechnik e.V.

This material was copied

**DOCKET  
ALARM**

Find authenticated court documents without watermarks at [docketalarm.com](http://docketalarm.com).

© 2011 Elsevier B.V. All rights reserved.

This journal and the individual contributions contained in it are protected under copyright by Elsevier B.V., and the following terms and conditions apply to their use:

**Photocopying**

Single photocopies of single articles may be made for personal use as allowed by national copyright laws. Permission of the publisher and payment of a fee is required for all other photocopying, including multiple or systematic copying, copying for advertising or promotional purposes, resale, and all forms of document delivery. Special rates are available for educational institutions that wish to make photocopies for non-profit educational classroom use.

For information on how to seek permission visit [www.elsevier.com/permissions](http://www.elsevier.com/permissions) or call: (+44) 1865 843830 (UK) / (+1) 215 239 8304 (USA).

**Derivative Works**

Subscribers may reproduce tables of contents or prepare lists of articles including abstracts for internal circulation within their institutions. Permission of the publisher is required for resale or distribution outside the institution.

Permission of the publisher is required for all other derivative works, including compilations and translations. (please consult [www.elsevier.com/permissions](http://www.elsevier.com/permissions)).

**Electronic Storage or Usage**

Permission of the publisher is required to store or use electronically any material contained in this journal, including any article or part of an article. (please consult [www.elsevier.com/permissions](http://www.elsevier.com/permissions)).

Except as outlined above, no part of this publication may be reproduced, stored in a retrieval system or transmitted in any form or by any means, electronic, mechanical, photocopying, recording or otherwise, without prior written permission of the publisher.

**Notice**

No responsibility is assumed by the publisher for any injury and/or damage to persons or property as a matter of products liability, negligence or otherwise, or from any use or operation of any methods, products, instructions or ideas contained in the material herein. Because of rapid advances in the medical sciences, in particular, independent verification of diagnoses and drug dosages should be made.

Although all advertising material is expected to conform to ethical (medical) standards, inclusion in this publication does not constitute a guarantee or endorsement of the quality or value of such product or of the claims made of it by its manufacturer.

**Funding body agreements and policies**

Elsevier has established agreements and developed policies to allow authors whose articles appear in journals published in Elsevier, to comply with potential manuscript archiving requirements as specified as conditions of their grant awards. To learn more about existing agreements and policies please visit <http://www.elsevier.com/fundingbodies>

Printed by Polestar Wheatons Ltd, Exeter, UK

---

*European Journal of Pharmaceutics and Biopharmaceutics* is the official journal of the Arbeitsgemeinschaft für Pharmazeutische Verfahrenstechnik (APV) e.V. Annual subscription: Euro 194/JPY 30,000 and US\$ 259. All prices plus postage. Special subscription rate for members of the American Association of Pharmaceutical Scientists, Associazione Docenti e Ricercatori Italiani di Tecnologia e Legislazione Farmaceutica (ADRITELF), the Controlled Release Society and the UK Association of Pharmaceutical Scientists: Euro 85 plus postage. Members of the APV receive the journal free-of-charge.

**Publication information:** *European Journal of Pharmaceutics and Biopharmaceutics* (ISSN 0939-6411) is published by Elsevier (Radarweg 29, 1043 NX Amsterdam, the Netherlands). Further information on this journal is available from the Publisher or from the Elsevier Customer Service Department nearest you or from this journal's website (<http://www.elsevier.com/locate/ejpb>). Information on other Elsevier products is available through Elsevier's website (<http://www.elsevier.com>). Periodicals Postage Paid at Rahway, NJ, and at additional mailing offices.

**Sponsored Supplements and/or Commercial Reprints:** For more information please contact Elsevier Life Sciences Commercial Sales, Radarweg 29, 1043 NX Amsterdam, The Netherlands; phone: (+31) (20) 485 2939/2059; e-mail: [LSCS@elsevier.com](mailto:LSCS@elsevier.com).

This material was copied



CONTENTS

Cited in: BIOSIS/Biological Abstracts, CAB Abstracts, Chemical Abstracts Service, EMBASE/Excerpta Medica, International Pharmaceutical Abstracts, PUBMED/MEDLINE/Index Medicus, PASCAL M, Science Citation Index Expanded. Also covered in the abstract and citation database SCOPUS®. Full text available on ScienceDirect®

Review article

Manufacture and characterization of mucoadhesive buccal films
J. O. Morales, J. T. McConville (USA) 187

Research papers

Reversible Targeting and controlled release delivery of daunorubicin to cancer cells by aptamer-wrapped carbon nanotubes
S. M. Taghdisi, P. Lavaee, M. Ramezani, K. Abnous (Iran) 200

Preclinical evaluation of tacrolimus colloidal dispersion for inhalation
A. B. Watts, J. I. Peters, R. L. Talbert, K. P. O'Donnell, J. J. Coalson, R. O. Williams III (USA) 207

In vitro and in vivo evaluation of WGA-carbopol modified liposomes as carriers for oral peptide delivery
A. Makhlof (Japan, Egypt), S. Fujimoto, Y. Tozuka, H. Takeuchi (Japan) 216

Thermosensitive hydrogels for nasal drug delivery: The formulation and characterisation of systems based on N-trimethyl chitosan chloride
H. Nazar, D. G. Fatouros, S. M. van der Merwe (UK), N. Bouropoulos, G. Avgouropoulos (Greece), J. Tsibouklis, M. Roldo (UK) 225

The design of flexible ciprofloxacin-loaded PLGA implants using a reversed phase separation/coacervation method
P. I. P. Park, M. Makoid, S. Jonnalagadda (USA) 233

Influence of adsorbents in transdermal matrix patches on the release and the physical state of ethinyl estradiol and levonorgestrel
M. Schulz, B. Fussnegger, R. Bodmeier (Germany) 240

The influence of positive or negative charges in the passive and iontophoretic skin penetration of porphyrins used in photodynamic therapy
G. M. Gelfuso, T. Gratieri, J. G. Souza, J. A. Thomazine, R. F. V. Lopez (Brazil) 249

Biorelevant in vitro dissolution testing of products containing micronized or nanosized fenofibrate with a view to predicting plasma profiles
D. Juenemann, E. Jantravid, C. Wagner (Germany), C. Reppas, M. Vertzoni (Greece), J. B. Dressman (Germany) 257

Uptake and permeability studies of BBB-targeting immunoliposomes using the hCMEC/D3 cell line
E. Markoutsas, G. Pampalakis, A. Niarakis (Greece), I. A. Romero (UK), B. Weksler (USA), P.-O. Couraud (France), S. G. Antimisiaris (Greece) 265

Identification of permeability-related hurdles in oral delivery of curcumin using the Caco-2 cell model
B. Wahlang, Y. B. Pawar, A. K. Bansal (India) 275

The production of 'aerodynamically equivalent' drug and excipient inhalable powders using a novel fractionation technique
M. Taki, C. Marriott (United Kingdom), X.-M. Zeng (USA), G. P. Martin (United Kingdom) 283

Ethylene vinyl acetate as matrix for oral sustained release dosage forms produced via hot-melt extrusion
A. Almeida, S. Possemiers, M. N. Boone, T. De Beer, T. Quinten, L. Van Hoorebeke, J. P. Remon, C. Vervaet (Belgium) 297

Novel extended-release formulation of lovastatin by one-step melt granulation: In vitro and in vivo evaluation
L. Ochoa, M. Igartua, R. M. Hernández, A. R. Gascón, M. A. Solinis, J. L. Pedraz (Spain) 306

Food-dependent disintegration of immediate release fosamprenavir tablets: In vitro evaluation using magnetic resonance imaging and a dynamic gastrointestinal system
J. Brouwers (Belgium), B. Anneveld, G.-J. Goudappel, G. Duchateau (The Netherlands), P. Annaert, P. Augustijns (Belgium), E. Zeijdner (The Netherlands) 313

Swelling kinetics of spray-dried chitosan acetate assessed by magnetic resonance imaging and their relation to drug release kinetics of chitosan matrix tablets
K. Huanbutta, P. Sriamornsak, S. Limmatvapirat, M. Luangtana-anan (Thailand), Y. Yoshihashi, E. Yonemochi, K. Terada (Japan), J. Nunthanid (Thailand) 320

Notes

Affinity and translocation relationships via hPEPT1 of H-Xaa-Ser-OH dipeptides: Evaluation of H-Phe-Ser-OH as a pro-moiety for ibuprofen and benzoic acid prodrugs
D. H. Omkvist, D. J. Trangbæk, J. Mildon, J. S. Paine, B. Brodin, M. Begtrup, C. U. Nielsen (Denmark) 327

Haloperidol-loaded polysorbate-coated polymeric nanocapsules increase its efficacy in the antipsychotic treatment in rats
D. M. Benvegnú, R. C. S. Barcelos, N. Boufleuer, P. Reckziegel, C. S. Pase, A. F. Ourique, R. C. R. Beck, M. E. Bürger (Brazil) 332

APV Diary 1

Calendar of Events II





Contents lists available at ScienceDirect

European Journal of Pharmaceutics and Biopharmaceutics

journal homepage: [www.elsevier.com/locate/ejpb](http://www.elsevier.com/locate/ejpb)

Review article

## Manufacture and characterization of mucoadhesive buccal films

Javier O. Morales, Jason T. McConville\*

College of Pharmacy, University of Texas at Austin, Austin, USA

### ARTICLE INFO

#### Article history:

Received 26 May 2010

Accepted in revised form 29 November 2010

Available online 3 December 2010

#### Keywords:

Buccal drug delivery

Oral mucosa

Mucoadhesion

Permeation

Mucoadhesive polymers

Buccal patches

### ABSTRACT

The buccal route of administration has a number of advantages including bypassing the gastrointestinal tract and the hepatic first pass effect. Mucoadhesive films are retentive dosage forms and release drug directly into a biological substrate. Furthermore, films have improved patient compliance due to their small size and reduced thickness, compared for example to lozenges and tablets. The development of mucoadhesive buccal films has increased dramatically over the past decade because it is a promising delivery alternative to various therapeutic classes including peptides, vaccines, and nanoparticles. The “film casting process” involves casting of aqueous solutions and/or organic solvents to yield films suitable for this administration route. Over the last decade, hot-melt extrusion has been explored as an alternative manufacturing process and has yielded promising results. Characterization of critical properties such as the mucoadhesive strength, drug content uniformity, and permeation rate represent the major research areas in the design of buccal films. This review will consider the literature that describes the manufacture and characterization of mucoadhesive buccal films.

© 2010 Elsevier B.V. All rights reserved.

### 1. Introduction

Films as dosage forms have gained relevance in the pharmaceutical arena as novel, patient friendly, convenient products. More recently, orally disintegrating films (or strips) have come to light, thanks to their improved mechanical properties [1]. This translates into a less friable dosage form compared to most commercialized orally disintegrating tablets, which usually require special packaging [2]. Mucoadhesive buccal films share some of these advantages and more. Due to their small size and thickness, they have improved patient compliance, compared to tablets [3–5]. Moreover, since mucoadhesion implies attachment to the buccal mucosa, films can be formulated to exhibit a systemic or local action [6]. Many mucoadhesive buccal films have been formulated to release drug locally in order to treat fungal infections in the oral cavity such as oral candidiasis [7–11]. Due to the versatility of the manufacturing processes, the release can be oriented either towards the buccal mucosa or towards the oral cavity; in this latter case, it can provide controlled release via gastrointestinal (GI) tract administration. Alternatively, films can be formulated to release the drug towards the buccal mucosa. Films releasing drug towards the buccal mucosa exhibit the advantage of avoiding the first pass effect by directing absorption through the venous system that drains from the cheek [12]. Previously, many articles have reviewed the

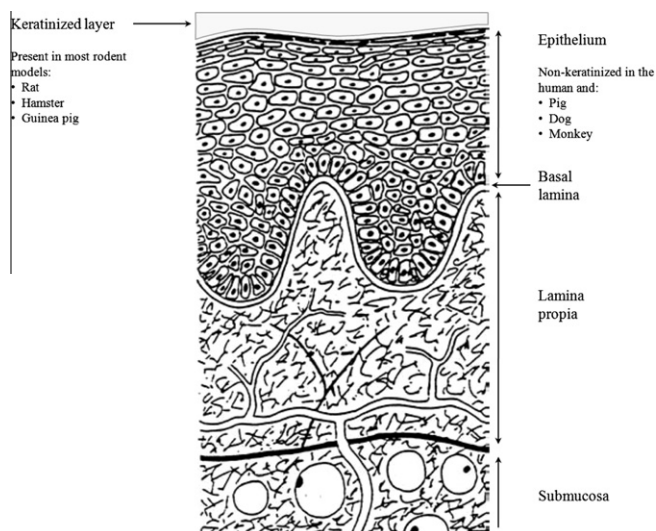
development of mucoadhesive buccal systems in global terms [13–17], or their specific attributes such as permeation enhancers [18] or mucoadhesive polymers [19–21]. This article reviews the relevant literature which provides a background for understanding the rationale behind the formulation of mucoadhesive buccal films, as well as reviewing the most crucial characterization techniques for these dosage forms. The reader should notice that the literature use the term film and patch interchangeably.

#### 1.1. Physicochemical properties of the oral mucosa

The oral mucosa presents differently depending on the region of the oral cavity being considered [22]. The masticatory mucosa covers those areas that are involved in mechanical processes, such as mastication or speech, and includes the gingival and hard palate. This masticatory region is stratified and has a keratinized layer on its surface, similar to the structure found at the epidermis, and covers about 25% of the oral cavity [23]. The specialized mucosa covers about 15%, corresponding to the dorsum of the tongue, and is a stratified tissue with keratinized as well as non-keratinized domains [24]. Finally, the lining mucosa covers the remaining 60% of the oral cavity, consisting of the inner cheeks, floor of the mouth, and underside of the tongue. This lining epithelium is stratified and non-keratinized on its surface [25]. The buccal mucosa covers the inner cheeks and is classified as part of the lining mucosa, having approximately 40–50 cell layers resulting in an epithelium 500–600 μm thick (Fig. 1) [26]. The epithelium is attached to underlying structures by a connective tissue or lamina propria, separated by a basal lamina. These lining mucosa and the lamina

\* Corresponding author. College of Pharmacy, University of Texas at Austin, 1 University Station A1920, Austin, TX 78712, United States. Tel.: +1 512 232 4088; fax: +1 512 471 7474.

E-mail address: [jtmconville@mail.utexas.edu](mailto:jtmconville@mail.utexas.edu) (J.T. McConville).



**Fig. 1.** Diagram of a cross section of the buccal mucosa. The keratinized layer is only present in most rodent models while the human has a non-keratinized buccal mucosa. Adapted from Ref. [39].

propria regions provide mostly mechanical support and no major barrier for penetration of actives [12,27]. The connective tissue also contains the blood vessels that drain into the lingual, facial, and retromandibular veins, which then open into the internal jugular vein [12]. This is one of the main advantages of buccal over oral delivery: absorption through the buccal epithelium avoids the gastrointestinal tract conditions, such as gastric pH, enzyme content, and the first pass effect due to direct absorption into the portal vein. Once a given drug molecule reaches the connective tissue, it may be readily distributed, thus the permeation barrier is across the whole thickness of the stratified epithelium [12].

The existence of membrane-coating granules in the epidermis has been well characterized and it is known to be the precursor of the keratin layer or stratum corneum [18,28]. Even though the existence of approximately 2  $\mu\text{m}$  in diameter cytoplasmic membrane-coating granules in the buccal epithelium has been proven, less is known in terms of their function; however, the permeation barrier is believed to be related to the presence of membrane-coating granules in the buccal mucosa [29,30]. Squier described these membrane-coating granules as organelles containing amorphous material that is extruded into the intercellular space after membrane fusion [29]. More recently, it has been reported that some of these granules also contain lipid lamellae domains organized to some extent [31]. This fact contrasts with the content of the membrane-coating granules in the epidermis, which contains very organized, electron-dense lipid lamellae. Therefore, the intercellular space of the stratified non-keratinized buccal mucosa is filled with a combination of amorphous material presenting some domains where short stack of lipid lamellae can be observed. This important difference in the intercellular space composition is responsible for the difference in permeability between the buccal and keratinized mucosae for exogenous compounds [32].

Although the buccal mucosa is more permeable than keratinized epithelium, the existence of a permeability barrier has been described [33]. It was demonstrated that this barrier is located in the upper one-third to one-quarter of the epithelium layer using horseradish peroxidase, and by following its permeation through the epithelium. After topical application, the horseradish peroxidase only permeated through the first 1–3 cell layers. However, when injected subepithelially, it was found to permeate through as deep as the connective tissue and up as far as the membrane

ity barrier is located in the upper region of the epithelium and is correlated with the rich lipid content of this zone. As well as the keratinized epithelium, the intercellular space of the buccal mucosa is rich in lipids, but it is the difference in composition and the absence of the keratin layer that accounts for its permeation characteristics [32,34–37]. The lipid composition in the buccal epithelium has a higher content of phospholipids, cholesterol esters, and glycosylceramides, while the content of ceramides is minimal, compared to the skin and keratinized regions of the oral cavity [32]. This composition results in a higher concentration of polar lipids in the intercellular space [34]. Therefore, it is not only due to the highly organized lipid lamellae found in the keratinized epithelia, but also the nature of the lipid content that accounts for the increased permeation of the buccal mucosa compared to the skin and other keratinized epithelia.

Due to the polar nature of the lipids in the intercellular space, two different domains can be differentiated in the buccal epithelium: the lipophilic domain, corresponding to the cell membranes of the stratified epithelium, and the hydrophilic domain, corresponding to the extruded content from the membrane-coating granules, into the intercellular space. These two domains have led to postulate the existence of different routes of transport through the buccal epithelium, namely the paracellular and the transcellular route [22]. The lipophilic nature of the cell membranes favors the pass of molecules with high  $\log P$  values across the cells. Similar to the absorption mechanism in the small intestine, it is believed that lipophilic molecules are carried through the cytoplasm [18]. However, there still is a lack of evidence supporting this assumption. The polar nature of the intercellular space favors the penetration of more hydrophilic molecules across a more tortuous and longer path [38–40]. It has been demonstrated that some hydrophilic molecules are subject to carrier-mediated transport through the buccal mucosa [41]. Most of the descriptions of molecules permeating through the buccal epithelium, in the literature, are related to the paracellular route of absorption. In an early study, it was found that tritiated water permeated through the paracellular route [36]. Using light microscopy autoradiography, it has been determined that water, ethanol, cholesterol, and thyrotropin release hormone penetrate through the paracellular route as well [42,43]. More recently, it was demonstrated using confocal laser scanning microscopy that dextrans with 4 and 10 kDa average molecular weight and labeled with fluorescein isothiocyanate permeated through the paracellular route [44,45]. Even though there is no evidence that supports the idea of molecules permeating through the transcellular route, it is important to assess and understand the permeation route in order to determine strategies to enhance the absorption of actives when formulating buccal films.

## 2. Formulation and manufacture of buccal delivery films

There are many factors in determining the optimum formulation of buccal delivery films, but three major areas have been extensively investigated in the mucoadhesive buccal film literature, namely mucoadhesive properties, permeation enhancement, and controlled release of drugs. Most of the polymers that are used as mucoadhesives are predominantly hydrophilic polymers that will swell and allow for chain interactions with the mucin molecules in the buccal mucosa [6]. Examples of these swellable polymers include hydroxypropyl cellulose (HPC), hydroxypropylmethyl cellulose (HPMC), hydroxyethyl cellulose (HEC), sodium carboxymethyl cellulose (SCMC), poly(vinyl pyrrolidone) (PVP), and chitosan; a full list of polymers used in the manufacture of buccal films, with additional descriptions and properties, is

# 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.