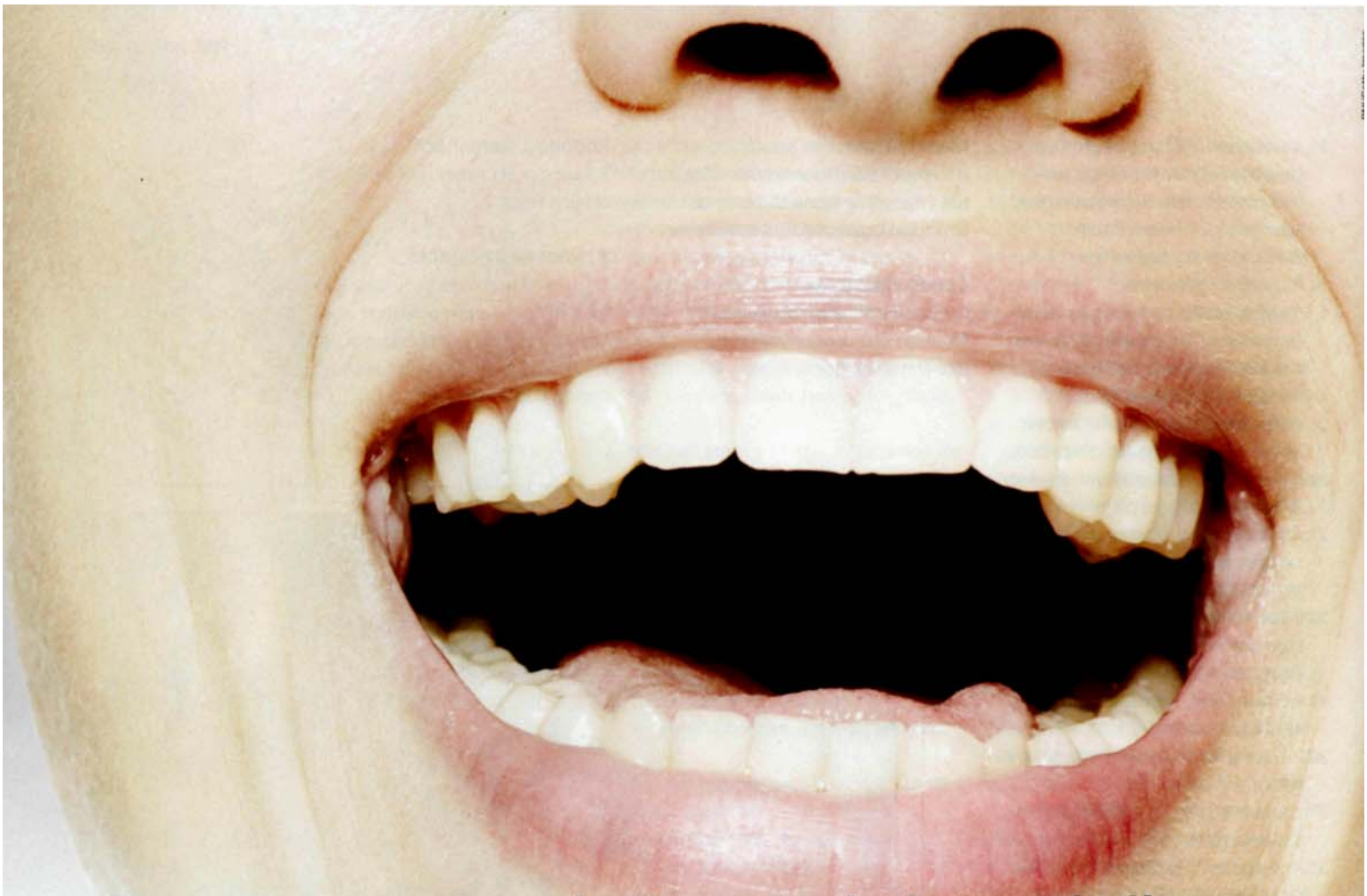


Current status in buccal drug delivery

This article analyses the progress made in buccal drug delivery research during the last 5 years and introduces a new high-tech approach to achieve controlled delivery.

Libero Italo Giannola
Viviana De Caro
Giulia Giandalia
Maria Gabriella Siragusa
Giuseppina Campisi
from University of Palermo.

Andy Wolff
from Assuta Hospital of Tel Aviv.

The adequate absorption and transport of drugs in the body is part of optimal therapy. Drug administration perorally is easy, common and traditional, but occasionally alternative routes are required. The major obstacles of this drug delivery method are the extensive presystemic degradation processes in the gut and/or liver, resulting in inadequate or erratic absorption and low systemic bioavailability. The parenteral route is the only established way that overcomes these drawbacks, but it may not achieve the maintenance of adequate drug levels at the receptor for as long as it is needed, which results in it high costs, poor patient compliance — especially in long-term therapies — and various further inconveniences and risks. Moreover, it requires repeated administration and is potentially hazardous as rapid drug removal is unachievable.

During the last two decades, transepithelial routes have been extensively explored by pharmaceutical researchers as alternative routes of delivery. Drug application to absorptive mucosae is often chosen to reach the site of action with little systemic drug concentrations to lessen side-effects.[1]

Among the various transepithelial sites available, the oral mucosa is the most convenient and accessible. If low drug concentrations are required to gain access to the blood, the transbuccal route may be very satisfactory, provided the physicochemical properties of a given drug allow permeation through the mucosa. Buccal delivery specifically refers to the delivery of drugs within/through the mucosa lining the inner cheeks. Compared with other mucosal tissues, buccal mucosa is more tolerant to potential allergens and has a lesser tendency to irreversible damage. Additionally, it is a well-vascularized, relatively immobile tissue and has relatively lower enzymatic activity.

Buccal mucosa allows drug delivery for both local and systemic therapies. Local delivery to tissues of the oral cavity has a number of applications, including treatment of local conditions such as periodontal disease, bacterial and fungal infections, aphthous stomatitis and vesiculo bullous diseases. When drugs are systemically administered through buccal mucosa, many drawbacks associated with the peroral route are circumvented as drugs directly enter the systemic circulation, avoiding the hepatic first pass metabolism and leading to high bioavailability. The buccal mucosa offers an easily accessible and generally well-accepted site for delivering systemically acting drugs mainly for the treatment of chronic diseases.[2–5]

Table 1 displays a nonexhaustive list of drugs investigated in buccal delivery systems.[6–15]

Buccal absorption

The principal mechanism of buccal absorption is passive diffusion. However, this assumption may be misleading as the oral mucosa contains active, carrier-mediated transport systems for few small molecules, such as monosaccharides and amino acids.[16] On occasion, absorption occurs by endocytosis where molecules are engulfed by the cells.[12] Two main pathways seem to be implicated in passive diffusion across mucosae: intracellular (or transcellular) and intercellular (or paracellular). Within the intercellular spaces there are two ways: one, hydrophobic, goes through the lipid domains; the other, hydrophilic, relates to the aqueous channels associated with the polar head groups of lipids and proteins. The intrinsic physicochemical properties of the drug, such as solubility, partitioning, stability, crystallinity, thermodynamic activity, molecular size, pKa and half-life, can constitute limiting factors to drug absorption:

- Low solubility determines a small concentration gradient to the plasma and the rate of diffusion is accordingly low.
- Highly lipophilic compounds could permeate through the transcellular route by partitioning into the lipids of the intercellular matrix while hydrophilic compounds could diffuse through the paracellular pathway. Some drugs can permeate using both routes simultaneously, but the route with the least penetration resistance is usually preferable.
- Crystalline status and thermodynamic activity of a drug are correlated with the diffusant concentration, thus affecting permeation.
- Small molecules, <~100 Da, cross the mucosa rapidly; permeability decreases as molecular size increases; high molecular weight drugs, such as peptides, oligonucleotides and hormones, usually have low permeability leading to a low bioavailability.
- The pKa is indicative of the molecule degree of ionization and affects permeability: maximum absorption occurs when molecules are not ionized and absorption decreases as the degree of ionization increases. Most drugs are weak acids or bases, and exist in solution as equilibrium between the unionized and ionized forms. Only unionized nonpolar drugs penetrate the membrane and, at equilibrium, the concentrations of the unionized species are equal on both sides of the membrane. The unionized form is assumed to be sufficiently lipophilic to cross membranes. The fraction ionized is controlled by both the environmental pH and the drug pKa.[17]

The physical state and composition of the formulation may affect dissolution rate. The physicochemical characteristics of the dosage form affect the rate and the amount of the released API, and primarily depend on

Table 1 List of APIs investigated for buccal delivery.

Acitretin	Acyclovir
Arecoline	Buprenorphine
Buserelin	Buspirone
Captopril	Carbamazepine
Carvedilol	Cetylpyridinium chloride
Chlorhexidine diacetate	Chlorpheniramine maleate
Clotrimazole	Cyanocobalamin
Danazol	Denbufylline
Diclofenac sodium	Diltiazem
Endomorphin 1	Ergotamine tartrate
Fentanyl	Flurbiprofen
Glucagon like peptide	Gonadotropin releasing hormone
Hydralazine	Hydrocortisone acetate
Ibuprofen	Insulin
Ketoprofen	Lactoferrin
Leu-enkephalin	Lidocaine
Lueinizing hormone releasing hormone	Melatonin
Metaclopromide	Metoprolol tartrate
Metronidazole	Miconazole
Morphine sulphate	Nalbuphine
Naltrexone	Nicotine
Nifedipine	Nimesulide
Nystatin	Octreotide acetate
Omeprazole	Oxytocin
Pentazocine	Pilocarpine
Pindolol	Piroxicam
Pituitary adenylate cyclase-activating polypeptide (PACAP)	Prednisolone
Propolis	Propranolol
Protrelin (TRH)	Recombinant human epidermal growth factor
Recombinant human interferon	Salmon calcitonin
Silymarin	Terbutaline sulphate
Testosterone	Theophylline
Thiocolchicoside	Thyotropin releasing hormone
Triamcinolone acetate	Verapamil

drug affinity to the vehicle. The permeation rate across the buccal mucosa can be satisfactorily modified by changing the composition and drug concentration in a formulation.[18]

Being absorption restrained by a diffusion process, the absorbing surface plays a key role. Most drugs administered as buccal solid formulations exhibit low bioavailability, mainly because of the relatively small area available for absorption. Semisolid formulations seem suitable for local treatments because they can be spread over a large portion of the mucosa.[18]

The drug vehicle has been suggested to be quite complex as it could affect membrane hydration, stimulate or prevent saliva secretion and interact with the local mucins. Wettability of soft tissues in the oral cavity can be expected to change greatly during the day under the influence of dietary components and oral hygiene measures.[19]

As the buccal mucosa is relatively immobile, the placement of retentive sustained-release transmucosal drug delivery systems is feasible and well-accepted by patients.[20] Vascularity and blood stream are also important because some drugs may cause vasoconstriction and limit drug absorption.

Some other less well-defined factors, such as the presence of a 3D mucus network, presence of bacteria, salivary flow rate, foods and involuntary swallowing, result in drug losses from the site of absorption. Injuries and disease states, where the mucosa is seriously damaged, would be expected to increase permeability (e.g., in conditions that result in erosion of the oral mucosa such as lichen planus, pemphigus, viral infections and allergic reactions).

Assessing drug permeation through the buccal mucosa

Given that the most important determinant of buccal delivery is the degree of permeability of the mucosa, comprehensive knowledge of permeability barrier, transport mechanisms and pathways is crucial in developing transbuccal formulations. Accordingly, the aptitude of a drug to penetrate the barrier should be assessed by *in vitro*, *ex vivo* or *in vivo* methods. Low availability of human buccal tissue for experimental use has led to the application of animal tissue resembling human mucosa to evaluate drug mucosal permeability. The main concern of choosing a particular animal model is the resemblance of its oral mucosa to the human one, both in ultrastructure and enzymatic activity. No animal can fully represent human tissues, but what is sought is an animal oral mucosa with equivalent physical and biochemical properties. Porcine buccal mucosa has been considered as a representative model as it resembles human tissue more closely than any other animal model in terms of lipid content and composition; membrane morphology and permeability barrier functions; composition and structure; and being nonkeratinized similar to human buccal mucosa.[21]

In the last decade, cultured normal (noncancerous) donated human cells grown on inserts at the air–liquid interface have been developed for rapidly and efficiently evaluating drug permeation across buccal mucosa.[22] Also, stratified cultured TR146 cell layers (so-called reconstituted human oral epithelium) have been suggested as a valuable new *in vitro* model for permeability studies, as they are analogous to normal human buccal epithelium. The cells, derived from a human neck metastasis originating from a buccal carcinoma, have been shown to grow on polycarbonate permeable inserts and form cell layers resembling

On the go...

- The buccal route may be very satisfactory for drug delivery, provided that the physicochemical properties of the drug allow permeation through the mucosa.
- Limited rate of buccal absorption could be adjusted by chemical or physical enhancement.
- Varieties of *in vitro* and *ex vivo* methods allow assessing the ability of drugs to cross buccal mucosa.
- The formulative approach alone is not sufficient for an effective control of drug delivery through the buccal mucosa.
- Complex high-tech devices, such as the IntelliDrug system, may provide the desired precise control and the most efficient therapeutic outcomes.

Table 2 List of molecules investigated as buccal permeation enhancers.

23-Lauryl ether	Benzalkonium chloride
Capric acid	Cetrimide
Cetylpyridinium chloride	Chitosan
Chitosan-4-thio-butylamidine	Chitosan-4-thioglycholic acid
Citric acid	Cyclodextrin
Dextran sulfate	Dodecylazacycloheptan-2-one (Azone)
EDTA	Glycol
Lauric acid	L-lysine
Lysalbinic acid	Lysophosphatidylcholine
Menthol	Methyloleate
Oleic acid	Phosphatidylcholine
Polyoxyethylene-20-cetyl ether	Poly-L-arginine
Polyoxyethylene	Polyoxyethylene-9-laurylether
Polysorbate 80	Sodium 5-methoxy salicylate
Sodium citrate	Sodium deoxycholate
Sodium EDTA	Sodium glycodeoxycholate
Sodium glycoholate	Sodium lauryl sulfate
Sodium salicylate	Sodium taurocholate
Sodium taurodeoxycholate	Sodium taurodihydrofusidate
Sodium tauroglycocholate	Sulfoxides
Unsaturated cyclic ureas	Various alkyl glycosides

the stratified human tissue. The model has similar morphology, ultrastructure and permeability barrier properties to intact buccal mucosa. Studies on bidirectional permeability have shown close correlation to the data obtained using human, monkey and porcine buccal mucosa.[23,24]

Various types of diffusion devices, including continuous flow perfusion chambers, using chambers, vertical and horizontal Franz cells, Grass–Sweetana diffusion chambers, Transwell and a choice of further side-by-side flow through cells, are commercially available for permeation studies — most of which have been used to determine the permeability of oral mucosa.[12]

Limitations

Similar to other mucosal membranes, the buccal mucosa has some disadvantages including short residence time and small absorption area. Moreover, the dosage form resides in a taste-sensing organ, and organoleptic aspects of formulation could become central and limiting factors for drug application. Suitable palatal properties are often required to improve acceptability of dosage form or to mask less desirable properties of the active component. Some additives should be incorporated to improve drug release and absorption, but the major limitation to buccal drug delivery is the barrier property of the tissue, which has inadequate permeability for certain molecules, resulting in low drug bioavailability.

Promoting buccal absorption

Permeation of drugs throughout epithelial barriers could be promoted by 'penetration enhancers' capable of decreasing the barrier properties of the mucosa by different mechanisms. Enhancement is founded on different techniques that are usually subdivided in chemical or physical methods.[6,25–28]

Chemical methods. Chemical enhancers are thought to improve absorption without irritation or damage of the mucosa by:

- Altering the rheology of the mucus layer.
- Transiently altering the lipid bilayer membrane.
- Increasing cell membrane fluidity.
- Extracting structural lipids.
- Altering cellular proteins.
- Increasing the thermodynamic activity of the permeant.
- Overcoming the enzymatic barrier.

Chemical enhancers could be added to a formulation, alone or in combination; their efficacy depends on the physicochemical properties of both the drug and the vehicle.

Various chelators, surfactants, bile salts and fatty acids have been used as permeation enhancers; chitosan and its derivates have been used as enhancers of small polar molecules and hydrophilic large molecules. Recently, lysalbinic acid, a product of the egg albumin hydrolysis, has been successfully used as an enhancer of peptide drugs.

Enzymatic drug inactivation is neither rapid nor extensive as the enzymatic activity of buccal mucosa is relatively low. Nevertheless, enzymes of the oral cavity could degrade some peptide and protein drugs. Co-administration of enzyme inhibitors, such as aprotinin, bestatin and puromycin, and bile salts could be effective as they reduce the activity of proteolytic enzymes. Table 2 shows a nonexhaustive list of molecules investigated as buccal permeation enhancers.

Physical methods. Enhancement can be obtained by a variety of techniques. Mechanically by:

- Removal of the outermost layers of the epithelium to decrease the barrier thickness.
- Sonophoresis (phonophoretic drug delivery) that provisionally reduces the density of the lipids domain as a result of micromechanical, thermal and cavitation effects.[29]

Electrically (when electric fields are applied to a mucosal membrane transport enhancement of ions can be provided) by:

- *Iontophoresis,* which is an effective and rapid method of delivering water-soluble, ionized or ionizable medications, and involves electrically induced transport by application of low level current.[30,31]
- *Electro-osmosis*, the process by which charged particles tend to migrate toward a less charged area.
- *Electro-poration*, the process by which a large electric pulse temporarily disturbs the membrane phospholipid bilayer allowing molecules permeation throughout the tissue.[32]

Table 3 List of polymers investigated as buccal mucoadhesive materials.

Agarose	Aminodextran
Carboxymethylcellulose (CMC)	Carragenan
Chitosan	Copolymer acrylic acid - PEG
Dimethylaminoethyl dextran	Gelatin
Gellan gum	Guar gum
Hakea gum	Hyaluronic acid
Hydroxyethyl cellulose	Hydroxyethyl methacrylate
Hydroxyethyl starch	Hydroxypropyl cellulose
Hydroxypropylmethyl cellulose	Hydroxypropylmethyl cellulose phthalate
Methyl cellulose	Methylhydroxyethyl cellulose
Palmitoyl glicol chitosan	Pectin
Poly (D,L-lactide co-glycolide)	Poly 2-hydroxyethyl methacrylate
Polyacrylic acid-co-ethylhexylacrylate	Polyalkylcyanoacrylate
Polymethylvinylether-co-methacrylic acid	Poly-N-2-hydroxypropyl methacrylamide
Polyacrylates	Polyacrylic acid
Polyoxyethylene	Polyvinyl alcohol
Polyvinyl pyrrolidone	Sodium alginate
Sodium CMC	Thiolated CMC
Xanthan gum	

Buccal delivery dosage forms

Many dosage forms have been developed including toothpastes, mouthwashes, lozenges, gels, ointments, wafers, microparticles, chewing gums, lollipops, films, patches, tablets and some specialized devices. Conventional dosage forms exhibit some drawbacks; for example, the low bioavailability as a result of the washing effect of saliva and mechanical stresses.

Unconventional dosage forms allow control of the buccal environment, optimization of drug permeation and governance of the drug dissolution rate. Formulations able to prolong the drug residence time on the absorptive tissue offer great advantages in promoting transmucosal delivery for systemic therapies. Recent research on mucoadhesive polymers has led to the development of several buccal delivery systems able to maintain a steady release of drug in the systemic circulation. Thanks to the lack of the transient spikes in drug concentration typical of daily multiple-dose regimens, these delivery systems decrease the risks of toxic side-effects. For efficient and prolonged release of drugs, these delivery systems must be in close contact with the mucosal membrane, which results in high concentration in a local area and high drug flux through the mucosa.[11–15,33–41]

Table 3 provides a nonexhaustive list of polymers investigated as buccal mucoadhesive materials.

Figure 1 A prototype of the IntelliDrug.

The IntelliDrug device

The 'IntelliDrug' device (Figure 1) represents a revolutionary method for delivering drugs for long-term chronic diseases through the buccal mucosa, according to the patient needs, in periods lasting days, weeks or months. The system, which is the size of two molars, consists of a stainless steel intra-oral module containing an osmotic membrane, a drug reservoir that could additionally contain a chemical enhancer, an actuation mechanism to push the drug solution, a drug level sensor, a flow sensor, a power source, software and an outlet system with iontophoresis electrodes (Figure 2).

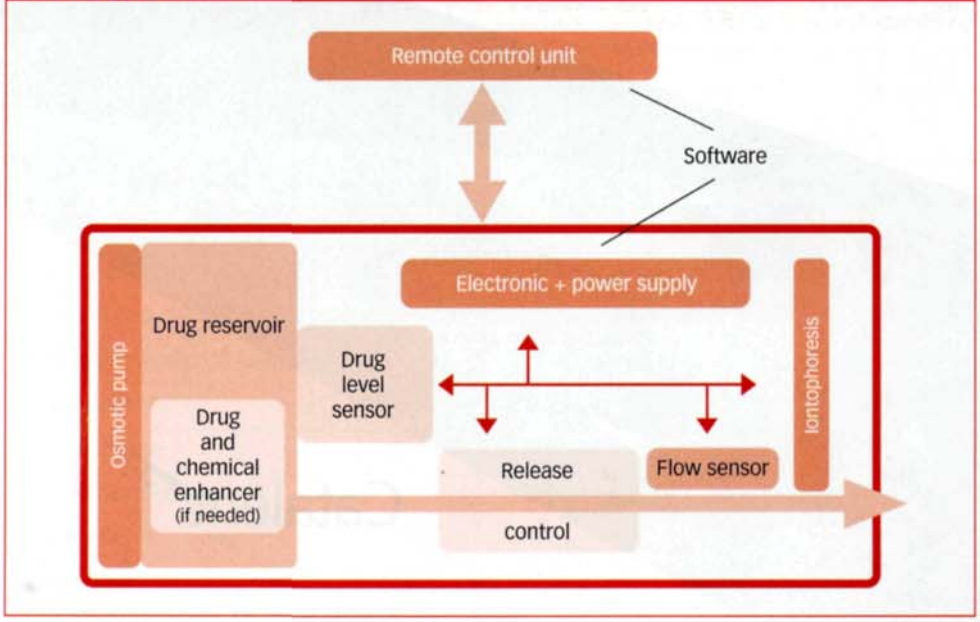
The drug is placed into the reservoir as a solid matrix. Water from saliva enters the system through the osmotic membrane on the lingual side of the device solubilizing the drug. The pressurized drug solution is released by a microvalve. A flow sensor combined with a concentration sensor allows metering of both the output flow rate of the drug solution on the buccal side and the depletion of the drug inside the reservoir. The device also incorporates electrodes for iontophoretic delivery enhancement.[42–44] This controlled drug delivery device can be implanted or inserted onto a prosthetic tooth crown, a denture plate, a dental implant, or the like, and refilled or replaced as required (Figure 3). The drug delivery may be passive or iontophoretically controlled.

The controlled delivery may follow any one of the following ways:

- In accordance with a preprogrammed regimen.
- At a controlled rate.
- Delayed.
- Pulsatile.
- Chronotherapeutic delivery.
- Responsive to a sensor input.
- On demand from a personal extracorporeal system.
- On demand from a monitoring centre, via a personal extracorporeal system.[45]

It is expected that patient compliance with such a system will strongly increase even though refilling of the device and battery replacement represent the greatest inconveniences of the system.

Figure 2 Schematic picture describing the most important components of the IntelliDrug device.



Conclusions

During the last decade, research on buccal drug delivery has revealed considerable growth and advances. Despite the advantages of delivering drugs through buccal mucosa, the formulative approach alone is not sufficient for an effective delivery control. The development of complex high-tech devices, which implies the confluence of very different competences, may give the desired precise control and the most therapeutic outcomes. Innovative high-tech products, such as the IntelliDrug system, could be a new challenge that is about to become more competitive. **PTE**

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Libero Italo Giannola

is Professor of pharmaceutical technology at the University of Palermo (Italy). He has more than 20 years of experience in various aspects of biopharmaceutics and pharmaceutical development. His research has been directed to develop novel drug delivery systems focused on nonconventional dosage forms for transepithelial drug absorption. Libero has extensively studied drug delivery and absorption through buccal mucosa and is Lead Scientist of the IntelliDrug Project.

Viviana De Caro

is Assistant Professor at the University of Palermo. She has focused her research on the development of drug delivery systems, putting her attention on the development of transepithelial topical systems.

Giulia Giandalia

is contractor at the University of Palermo. She has focused her research on the development of drug delivery through transepithelial routes.

Maria Gabriella Siragusa

is a PhD student at the University of Palermo. She is focusing her research on development of drug delivery systems for topical treatment of squamous carcinoma of buccal mucosa.

Giuseppina Campisi

is Professor in the Department of Oral Sciences at the University of Palermo. She is an expert in the management of patients with oral lichen planus and in topical therapy of oral diseases. Currently, Guiseppina and her group work on buccal drug delivery for chronic assumption. She is Project Manager of the IntelliDrug project.

Andy Wolff

is a dentist and specialist in oral medicine and was the Head of the Dentistry Department at Assuta Hospital in Tel Aviv (Israel). He holds a series of patents in the area of intra-oral electronic medical devices. Currently, Andy is the Scientific Director of the IntelliDrug project.

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Figure 3 A prototype of the IntelliDrug device embedded in a partial lower jaw denture.