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Drug delivery from the oral cavity: focus on a novel mechatronic delivery device

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Dental drug delivery systems have been used for a long time, in particular for the local therapy of diseases affecting the oral cavity. Research today concentrates on the design of formulations to increase their retention time. Even today, however, prosthetic devices incorporating drug delivery are rarely used. Mainly, they are focused on prophylaxis and the release of antibacterial agents. However, as buccal delivery, because of its undeniable advantages, has become popular for systemic drug delivery, and prolonged well-controlled release has been identified as beneficial, especially for chronic diseases, a new class of delivery systems is evolving: highly miniaturized computerized delivery systems, integrated into a dental appliance. Dental delivery systems today are used in two ways: the main application is the local treatment of diseases affecting the oral cavity itself like periodontitis or fungal infections. The second is for systemic drug delivery.

Intraoral systemic drug delivery

Generally, the peroral route is considered the most convenient route for drug delivery by patients and clinicians. However, this route has several potential disadvantages, such as extensive hepatic first-pass metabolism and presystemic drug degradation in the gastrointestinal tract, which results in compromised dosing accuracy, low drug availability at the site of action and the necessity for frequent administration. The parenteral route of administration is the only established route that overcomes all these drawbacks. Even though, for controlled release of solid systems (e.g. injectable and totally biodegradable hypodermic polymeric devices), the parenteral route may give excellent drug bioavailability, it can suffer from poor patient compliance and various risks, such as anaphylaxis and extravasation infection. These limitations have driven the development of alternative administration routes with the absorptive mucosae attracting extensive research, as they offer many benefits, such as noninvasive administration, rapid onset of effect, good bioavailability, elimination of hepatic first-pass metabolism, reduced amount of administered drug and low-dose-related side effects. Of the nonperoral routes, trans-buccal mucosal routes have become one of the most popular for systemic drug delivery, behind pulmonary delivery, but the anatomical properties and the environmental conditions of the oral cavity need careful consideration in order to increase efficacy successfully [1,2].

The environment of the oral cavity

The environment of the oral mucosa and its composition has been well studied [3–5]. Its main characteristics are the continued secretion of saliva from major and minor salivary glands. Oral fluid can be considered the protective fluid for all tissues of the oral cavity. It acts as a buffer, maintaining a pH range from 5.75 to 7.05 [6] and is mainly composed of water (99.5%), organic compounds (0.3%), inorganic and trace elements (0.2%) [7]. For artificial items

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1359-6446/06/$ - see front matter doi:10.1016/j.drudis.2007.10.018

inside the mouth, for example, prosthetic or orthodontic devices, the environmental conditions inside a human's mouth are harsh: the humidity is mostly 100%. The temperature, though generally around 37 °C, can vary between +5 and +55 °C for short times at least, for example, when eating or drinking cold or hot meals or beverages. Mastication can generate forces of up to 500 N and abrasion can occur on the teeth and on any item that resembles a chewing surface. Despite its buffering properties, salivary pH can drop as low as 2 when consuming acidic drinks. Moreover, the healthy oral cavity is colonized by microorganisms like fungi, viruses and bacteria, of which more than 700 species or phylotypes have been detected in the oral cavity [8]. Special attention must, therefore, be paid to the hygiene requirements of an artificial device inside the mouth.

Delivery from the oral cavity

In the oral cavity, regions where effective drug delivery can be achieved are buccal, sublingual, palatal and gingival. Buccal and sublingual sectors are the most appropriate for drug delivery and they may be used for the treatment of local or systemic diseases. The sublingual mucosa is more permeable and thinner than the buccal mucosa and, because of the considerable surface area and high blood flow, it is a feasible site when a rapid onset is desired. The sublingual route is generally used for drug delivery in the treatment of acute disorders, but it is not always useful because its surface is constantly washed by saliva, and tongue activity makes it difficult to keep the dosage form in contact with the mucosa for an extended period of time. Unlike the sublingual mucosa, the buccal mucosa offers many advantages because of its smooth and relatively immobile surface and its suitability for the placement of a retentive sustained- or controlled-release system, well accepted by patients.

The buccal mucosa is a useful route for the treatment of either local or systemic therapies overcoming the drawbacks of conventional administration routes. The buccal mucosa is relatively permeable, robust and, in comparison with other mucosal tissues, is more tolerant to potential allergens and has a reduced tendency to irreversible irritation or damage. So, it has been largely investigated as a potential site for controlled drug delivery in various chronic systemic therapies.

However, salivary production and composition may contribute to chemical modification of certain drugs [9]; moreover, involuntary swallowing can result in drug loss from the site of absorption. Furthermore, constant salivary scavenging within the oral cavity makes it very difficult for dosage forms to be retained for an extended period of time in order to facilitate absorption in this site. The relatively small absorption area and the barrier property of the buccal mucosa contribute to the inherent limitations of this delivery route.

Enhancement of trans-mucosal agent transport

Nonenhanced drug delivery is based solely on diffusion. Hydrophilic, ionic drugs usually diffuse through the intercellular space, while hydrophobic are able to pass through cellular membranes. Depending on physico-chemical properties of the drug, the buccal mucosa may have insufficient permeability and could represent a major limitation in the development of a buccal drug delivery system. In addition, the limitation of the available absorption area and the short time of exposure, because of the washing effect of saliva, can decrease absorption efficiency even more.

Permeation of drugs throughout epithelial barriers could be promoted by 'penetration enhancers' utilizing different techniques, usually subdivided into chemical or physical methods. Buccal penetration enhancers are capable of decreasing the barrier properties of the buccal mucosa by increasing cell membrane fluidity, extracting the structural intercellular and/or intracellular lipids, altering cellular proteins, or altering the mucus structure and rheology [10–12].

Chemical penetration enhancers

Chemical enhancers could be added to a pharmaceutical formulation, alone or in combination, in order to increase the permeation rate, without damage to, or irritation of, the mucosa. Enhancer efficacy depends on the physico-chemical properties of the drug, the administration site and the nature of the vehicle. Penetration enhancers are thought to improve mucosal absorption by different mechanisms, for example, reducing the viscosity and/or elasticity of the mucus layer, or by transiently altering the lipid bilayer membrane, or overcoming the enzymatic barrier, or increasing the thermodynamic activity of the permeant.

Various chemicals have been used as permeation enhancers across the epithelial tissues; among them chelators (e.g. sodium EDTA or salicylates), surfactants (e.g. sodium dodecyl sulfate, polyoxyethylene-9-lauryl ether, polyoxyethylene-20-cetyl ether and benzalkonium chloride), bile salts (e.g. sodium deoxycholate, sodium glycocholate, sodium taurocholate and sodium glycodeoxycholate), fatty acids (e.g. oleic acid, capric acid and lauric acid) and nonsurfactants (e.g. ciclodextrins and Azones®) [10,11]. Recently, chitosan and its derivates have been extensively used to enhance permeation across either monostratified or pluristratified epithelia of small polar molecules and hydrophilic large molecules either in animal models or in human beings [13].

The enzymatic activity of the buccal mucosa is relatively low, and drug inactivation is neither rapid nor extensive. Nevertheless, enzymes existing in the oral cavity could degrade some drugs, particularly peptide or protein drugs. Coadministration of enzyme inhibitors such as aprotinin, bestatin, puromycin and bile salts reduces the activity of proteolytic enzymes, altering the conformation of the peptide drug or forming micelles, and/or rendering the drug less accessible to enzymatic degradation.

Mechanical penetration enhancers

Drug absorption can also be enhanced mechanically, for example, by removing the outermost layers from epithelium to decrease the barrier thickness, or electrically, for example, by application of electric fields or by sonophoresis. The latter acts by reducing, temporarily, the density of lipids in the intercellular domain of the membrane. This 'disruption' occurs due to a combination of micromechanical, thermic and cavitation effects that effectively 'open up' the intracellular pathways, allowing substances to penetrate.

After chemical enhancement, the most efficient permeation enhancement methods for intraoral applications are probably the electrical mechanisms, such as electrophoresis (iontophoresis), electro-osmosis and electroporation.

Electrophoretic enhancement in the oral cavity has been reported for a number of applications [14]. It is most effective for water-soluble, ionized compounds. The rate of migration is limited by the maximum electric current which can be applied across the mucosa; generally, currents below 0.5 mA/cm^2 can be applied without adverse effects [15].

Another means of increasing the drug transport rate is by utilizing electro-osmosis. Human tissue possesses fixed negative charge, and binds mobile, positive, counterions, forming an electrically charged double layer in the tissue capillaries. When an electric field is applied across the tissue, there is a net flow of water through the tissue through the migration of the mobile solvated counterion, a process known as electro-osmosis. Drugs dissolved in the interstitial water are, hence, transported into the tissue by bulk flow.

In electroporation, very short (10 μs to 1 ms) high potential (20–100 V) pulses are applied across the tissue. Due to electrostriction forces, cellular membranes are temporarily perforated or even microchannels in the tissue are formed. Those channels serve as a drug transport route and are closed within few minutes without any lasting damage to the tissue [10,13,16].

Applications

Local drug delivery

More than a few conventional and unconventional dosage forms are dedicated to the delivery, within the oral cavity, for various local therapeutic applications, including the treatment of toothache, bacterial and fungal infections, aphthous ulcers, lichen planus, inflammation and dental stomatitis. Moreover, regional delivery of drugs in the periodontal pocket for the prevention and treatment of caries and periodontal diseases could be achieved by administering specialized dosage forms [17,18].

The reason for the large interest in the local treatment of the oral cavity diseases is a result of their being amongst the most prevalent in humankind. Almost every individual is affected by some kind of gingival disease and most human beings suffer from dental caries. Moreover, oral cancer is amongst the most frequent types of malignancies. Traditional treatment of oral disease is extremely costly, the fourth most expensive disease to treat in most industrialized countries, according to the WHO (see http://www.who.int/oral_health/disease_burden/global/en/index.html).

Many oral diseases are chronic and, hence, require chronic treatment regimens. In addition, most oral diseases can be treated locally, without the need for ingestion and systemic distribution of drugs. However, drug concentrations that can be achieved in the oral cavity are limited by taste sensation, restricting the value of this route of administration.

One way of overcoming this limitation is to prolong the contact time between the diseased tissue and the therapeutic agent [19]. However, therapeutic agents are usually delivered as mouthwashes, lozenges or gels. Thus, prolonged administration of these agents can become quite a tedious task for patients. As a result, compliance is poor and therapy efficacy very low, leading to high failure rate of oral treatments. Thus, very often, oral diseases that could be cured by pharmacological means are chronically carried by the patient [20]. This may be one of the reasons for the high prevalence of chronic oral diseases, such as periodontal disease, dental caries and lichen planus.

Buccal delivery for systemic therapy

Despite the obstacles for trans-mucosal drug delivery mentioned above, the buccal mucosa remains an attractive site for the delivery of systemic drugs, in particular for those who are prone to a high level of degradation inside the gastrointestinal tract. Various buccal delivery applications have thus been marketed or proposed in treatment of systemic and chronic diseases. Among them: trigeminal neuralgia, Ménière's disease, diabetes, addiction and so on [2,21–27]. Similar to the treatment of diseases affecting the oral cavity, intraoral systemic drug delivery would benefit from sustained drug release, without the need for the patient to intervene. This would raise the patient compliance particularly of chronically ill.

Chrono-therapy

There is one evolving application that can be interesting for intraoral delivery: certain fatal biological events, such as an acute myocardial infarction, display circadian variation in timing [28,29]. Consequently, one may suggest, and there is evidence [30], that the administration of pharmaceutical agents at a particular time of day could increase the efficacy of preventive medication. The scheduling of medicinal administration for optimized efficacy is generally termed 'chrono-therapy'. To facilitate this, chronically ill or high-risk patients need to adhere strictly to timed medication. It is difficult to realize tightly scheduled medication by standard pharmaceutical administration because compliance is frequently poor. A device that takes over this task for a sustained time period of days or weeks without requiring much effort by the patient would, thus, not only increase comfort and thus patient compliance, but also increase the efficacy of the therapy. It is obvious that this can only be realized by a programmable drug delivery system that can release pharmaceutical substances at a determined time.

Developments

Some factors that influence drug release within and through buccal mucosa and affect the therapeutic efficacy should be considered in the formulation design. Organoleptic aspects become central factors because the dosage form is to be resident in a taste-sensing organ. Excipients enhancing palatial properties are often required to improve the acceptability of a dosage form or masking less desirable properties of the active component. Some additives should be incorporated to improve drug release pattern and absorption. Many dosage forms have been developed and include toothpastes, mouthwashes, lozenges, gels, chewing gums, lollipops, films, patches, tablets and some specialized devices [31]. Conventional dosage forms, however, exhibit some drawbacks, for example, low bioavailability, because of the washing effect of saliva and mechanical stresses. Formulations that prolong the drug release in the mouth offer great advantages in preventing and treating local diseases or in promoting trans-mucosal delivery of drugs for systemic therapies.

The buccal mucosa is a feasible site for application of sustained- or controlled-release delivery systems which could maintain a steady release of drug in the systemic circulation thus avoiding the typical transient spikes in drug concentration of multiple-dose regimens and decreasing the risks of toxic side effects. For efficient and prolonged release of drugs, these delivery systems have to be

in close contact with the mucosal membrane, resulting in high concentration in a local area, prolonged residence time at the absorption site, and hence high drug flux through the absorptive mucosa. Recent research on the use of mucoadhesive polymer delivery systems for the mouth has led to the preparation of inserts for treatment of various diseases and several mucoadhesive buccal dosage forms have been developed [2,32,33].

Although sustained-release devices are a relatively new concept in dentistry, several types of devices are commercially available, or are in the premarketing stage. Drug-loaded polymeric matrices have been used for the controlled buccal delivery of antimicrobial, antibiotic, local anesthetic, antifungal and antiviral drugs. Composite filling materials (compomers) have been used to release fluoride ions in dental caries and a wide range of biomaterials, including polymeric hydrogels, porous scaffolds, nanofibers and microparticles have been utilized toward the regeneration of tooth, periodontal ligament, salivary gland, cranial sutures and the temporomandibular joint [17,34–36].

A pioneering sustained-release device for delivering a beneficial agent into the oral cavity is described by the US patent 5,512,293 by Alza Corporation. The invention relates to a device comprising about 0.1–20% (w/w) of active ingredient and about 40–95% (w/w) of ethylene [37]. Another invention by Alza Corporation involves the use of a bioerodible oligomer, or polymer, which can deliver a drug (e.g. an antibiotic) into the periodontal pocket. The material is heated and injected into the tissue pocket where it hardens and hence is retained in position. The material bioerodes in the pocket releasing the drug over a period of several days [38].

An implantable antimicrobial delivery device for the treatment of periodontal disease was prepared by the compression of drug-loaded microspheres. The delivery profile could be tuned by adjusting the degree of compression to match clinical needs. The device enables customization with respect to pocket size. The efficacy and safety of the delivery device has been established in canine and primate models [39].

A novel microparticulate delivery system, composed of poly(D,L-lactide-*co*-glycolide) and/or poly(ε-caprolactone) microspheres is effective in controlled delivery of doxycycline to periodontal pockets [40].

Only a few intraoral drug delivery devices have been reported that are not based exclusively on a chemical means of release. Among these are medical and dental implant devices that have been designed for controlled release of therapeutic and prophylactic agents and, in particular, prosthetic or combination implants for replacing, augmenting, or promoting the health of bone, cartilage, or dental tissues.

The international patent WO/2007/001624 describes a monolithic implantable dental device that includes a body adapted for insertion into one or more channels or voids in bone tissue. The device contains a plurality of discrete reservoirs and one release system containing at least one drug, for example, bone growth promoters, angiogenesis promoters, analgesics, anesthetics, antibiotics and combinations [41].

Certain conventional prosthetic devices may be provided with a coating comprising an antibiotic or growth factor. The device described by the international patent WO/2006/050106 includes a prosthetic device body having at least one outer surface area, discrete reservoirs spatially separated over the outer surface area. The reservoirs are formed with an opening at the surface of the device body. The system comprises one or more therapeutic or prophylactic agent, which are released in a controlled manner from the reservoirs [42].

It is plausible to assume that increased response rate can be achieved by improving the delivery method. An ideal drug administration system to treat both oral and nonoral diseases should fulfil the following criteria:

- It should be able to release medication in a continuous, or at least prolonged, pattern.
- It should deliver the medication in pulses that are controllable and programmable with respect to concentration and time.
- It should provide a high efficacy of drug delivery to minimize side effects.
- It should function automatically, in order to reduce patient burden for selfadministration.
- It should not impair the patient's comfort – taste, sensation and activities.
- It should not present any source of additional risk to the patient.

To our knowledge, only a delivery system driven by electronics and software, that is, a mechatronic approach, would be capable of fulfilling all of the above-mentioned requirements.

The 'IntelliDrug' device

An invention directed toward this ideal is reported in the international patent WO2004069076 that describes controlled drug delivery oral devices to be implanted into the oral cavity, built onto a prosthetic tooth crown or embedded inside a denture [43]. Recently, this patent, following a mechatronic approach, has been implemented within a European framework six IST project, dubbed 'IntelliDrug' [44] (Figs 1 and 2): a chamber (1) having the size of two molar teeth accommodates a drug reservoir (2), a microfluidic duct (3), an electrically controllable valve (4), sensors (5), electronics (6) and two batteries (7). The chamber (1) itself, fabricated of a medical grade stainless steel (Sandvik Bioline, Sandvik AB, Sandviken, Sweden), is designed to withstand forces encountered during mastication. The drug is placed into the device's reservoir as a solid pill (8). The driving force to release the substance is osmotic pressure, built up by an osmotic pumping section; water from the saliva enters the system through an osmotic membrane (9) on the lingual side of the device and generates a pressure in the drug reservoir (2), where it is stored by compressing a defined volume of air that is encapsulated in a polymer balloon (10). The pressurized drug solution can be released by switching a microvalve (4) that is normally closed because of medical safety reasons. In order to keep the energy consumption of the device and the required actuation voltages at a minimum, polypyrrole (PPy), an ionic electroactive polymer, was selected as actuator material of the valve [45]. The implementation of a flow sensor in combination with a concentration sensor allows the metering of both, the flow rate of the solution exiting the device output on the buccal side, and secondly the concentration of the drug solution which is used to detect the depletion of the drug pill inside the reservoir. The flow sensor utilizes the heat transfer principle and is capable of measuring a flow of up to 50 μl/h. The concentration sensor incorporates two interdigital electrode structures that are used to gauge the electrical impedance of

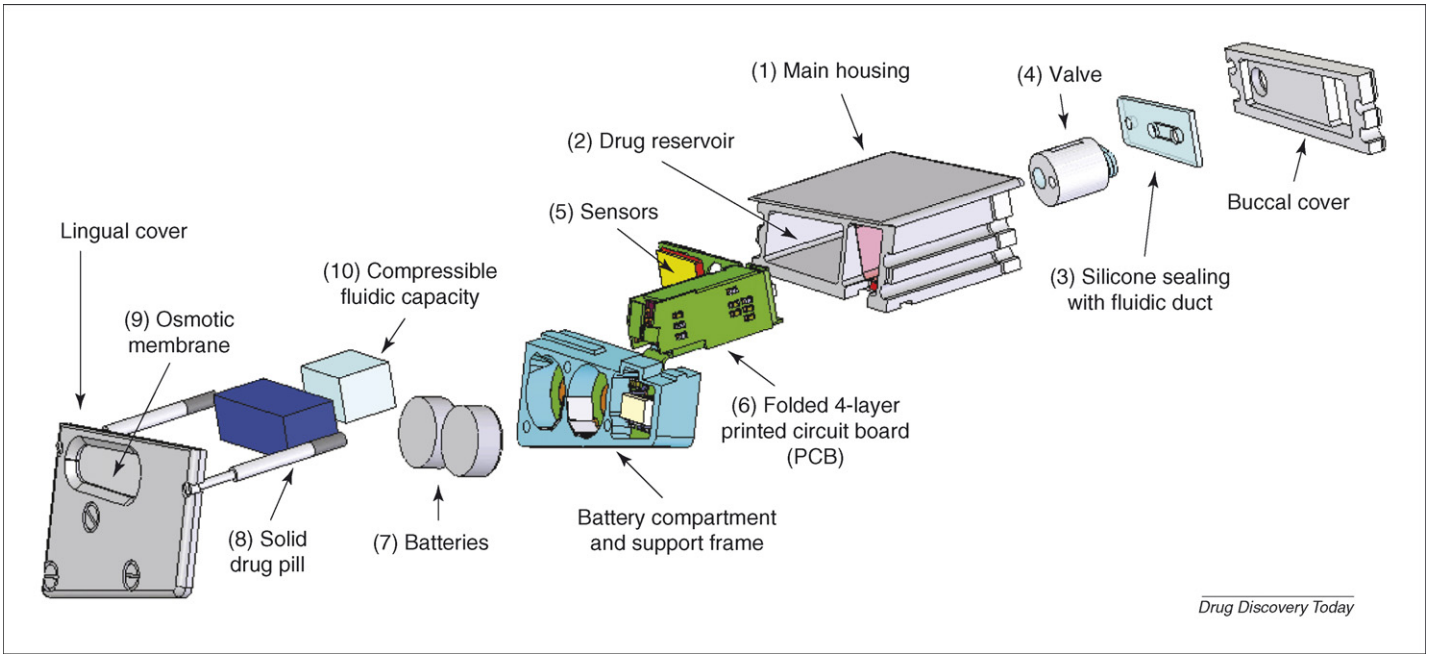

FIGURE 1

Exploded view of the 'IntelliDrug' delivery system, designed for the lower left cheek.

the electrode/solution interface. This, in turn, is related to the concentration level of the drug solution [46].

The main route of delivery, the design is targeted at, is buccal delivery. The device also incorporates an iontophoretic delivery enhancement by a coaxial electrode ring around the outlet. The rate of drug release is governed by the on-board electronics that modify the duty cycle of the valve openings. The user – either patient or physician – can control the whole device via an infrared remote control that enables him/her to program the dosage and monitor the status of the device, for example, the remaining drug level. It is estimated that the volume of the drug pill, measuring 116 mm^3, and the two zinc silver button cells (*SR421SW* Hitachi Maxell Ltd, Tokyo, Japan) of 1.55 V each, permit an operating time of the device of at least two weeks when being used with naltrexone hydrochloride (NTX), the substance which the device is designed to deliver. NTX is being administered to drug addicts after they have been undergoing detoxification in order to prevent relapse. That NTX can be efficiently administered via the buccal mucosa has been demonstrated *in vitro* [26] and in an animal study on pigs [47].

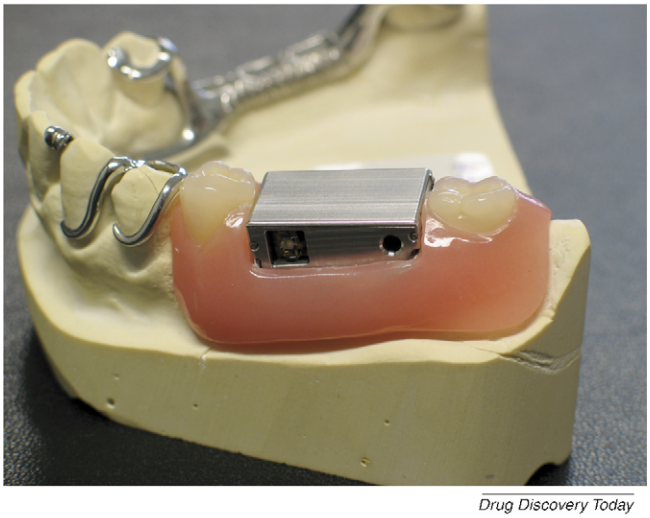

FIGURE 2

A nonminiaturized 'IntelliDrug' prototype embedded in a partial lower jaw denture.

As patient safety is a big concern several precautions have been taken to reduce hazards to an absolute minimum, for example, the release rate of the pill inside the reservoir is not sufficient to harm a patient even when the pill is swallowed. In general, the selection of medical substances suitable for the administration through IntelliDrug has to take safety issues into account.

Compared to dental delivery systems that only rely on chemically/physically controlled drug release, it does have some disadvantages: as described in [44], a patient who is able to wear the IntelliDrug device needs two missing adjacent teeth. This truly is a big disadvantage and limits the number of patients to those of poor dental health status or elder people who have already lost numerous teeth. This may be the case for a large number of Alzheimer patients and drug addicts. However, for other diseases the relative number of patients prepared to wear such a device may be significantly lower. If, by further technical improvement and miniaturization, the space requirement should decrease to a single molar, then it is conceivable that the number of those who could benefit from such an 'intelligent' dental prosthetic drug delivery system will increase, because a great proportion of adults lack at least one tooth.

Probably the biggest disadvantage of a dental prosthetic drug delivery system that follows a mechatronic approach is related to cost. First, the dosage form has to deviate from standard oral dosage forms so that it complies with the device, which will

increase cost. Secondly, the device is a complex and highly integrated system; however, the purchase will not be the biggest expense. The frequent maintenance (refilling of pharmaceutical, replacement of batteries) is likely to represent the greatest cost over a period of time.

Nevertheless, such a system has many advantages: using electronics, additional permeation enhancement can be easily added, for example, iontophoresis. It is expected that patient compliance with such a system will strongly increase. Constant daily drug levels are always achievable because prostheses are usually worn every day. Dose-related side effects are likely to decrease, enhancing compliance, because the administered dosage can be much better controlled and individually adjusted.

A computerized drug delivery system with on-board sensors *per se* gives much better control of the administered dosage. In addition, the dosage can easily be tailored to each individual patient. However, it is not clear yet by how much the plasma level will vary with buccal delivery. A closed loop control being the optimum would require sensors measuring the plasma level *in vivo* or indicators thereof.

This mechatronic approach enables the physician not only to precisely determine the absolute amount of pharmaceutic agent to be released into the body, but also lets him exactly schedule when the substance is to be released, thus enabling chrono-therapy for intraoral administration. By using electronically driven drug delivery, one could even add additional, beneficial communication features like patient- or point of care-supervision and intervention during the process of drug delivery. This can be achieved by wireless communication devices (personal proxy units) such as remote controls or cellular phones.

Conclusion

The oral cavity has long been a site of medicinal application in order to treat diseases in the mouth itself. Here, considerable improvements have been made in long-sustained delivery. The oral trans-mucosal route is becoming more and more popular for systemic drug delivery because it does have significant advantages compared to the peroral route. The grand majority of devices utilize solely chemical/physical released control to adjust the release rate. However, the control is rather limited compared to an active, mechatronic, drug delivery system being processor controlled. To the very best knowledge of the authors, the only existing orally based mechatronic device today is IntelliDrug. It thus belongs to a new class of oral delivery systems that have the promise, in the future, of providing an ideal drug delivery system.

Acknowledgements

The authors acknowledge the support of the whole IntelliDrug study group,[7] in particular Thorsten Göttsche (Hahn-Schickard-Gesellschaft, IMIT) for his contribution to this article as well as to the engineering work and Ben Z. Beiski, Assuta Medical Centers and Saliwell Ltd, for Project Management. Other valuable contributors to the project are the Project Officer Mr Thomas Sommer, Information Society and Media Directorate-General, European Commission (which funded the project under FP6), and the reviewers Prof. Jörgen Ekström, Institute of Neuroscience and Physiology, The Sahlgrenska Academy at Göteborg University, Sweden, and Prof. Dr Michiel J. Vellekoop, Institute of Sensor and Actuator Systems, Vienna University of Technology, Austria.

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